The New England
Journal of Medicine

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Volume 247 OCTOBER 9, 1952 Number 15

TREATMENT OF MENINGITIS DUE TO *HAEMOPHILUS INFLUENZAE**

Use of Chloromycetin and Sulfadiazine

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THE treatment of meningitis due to *Haemophilus influenzae* has undergone considerable change in the past fifteen years. Prior to the advent of specific therapy, this disease was fatal in 90 to 100 per cent of cases, and in the rare cases in which recovery took place, severe neurologic sequelae were frequently encountered. Wilkes-Weiss and Huntington,[1] in a review of the literature in 1936, reported 500 cases in patients of all ages, with a mortality of 92.2 per cent.

The introduction of Fothergill's specific antiserum and complement, together with the sulfonamide drugs, represented a considerable advance in the therapy of this type of meningitis. Lindsay, Rice and Selinger,[2] reviewing results obtained with this combination therapy, reported a mortality of 53.8 per cent. Even more progress was observed after the introduction of Alexander's[3] rabbit antiserum in 1939, which, in combination with sulfonamides, constituted the most effective modality of therapy[4] until the advent of streptomycin in 1945. Hewitt and Pittman[5] reported that most of the strains of *H. influenzae* were sensitive to streptomycin in a concentration of 2.5 microgm. per cubic centimeter or less. Weinstein[6] treated a series of 9 patients with streptomycin alone, with a mortality of 22 per cent. Alexander et al.[7] concluded from a study of 25 cases that streptomycin alone may produce recoveries in meningitis due to *H. influenzae* when the infection is of average severity; however, in severe infections a combination of rabbit antiserum, sulfadiazine and streptomycin was suggested as the treatment of choice.

The results at the Children's Hospital, Washington, D. C., supported the view that combined therapy was preferable to streptomycin alone. From 1948 to 1950, 30 patients were treated at the Children's Hospital with various combinations of streptomycin, sulfadiazine and Alexander's rabbit antiserum. The mortality in this series was 12 per cent.[8]

However, the employment of these drugs in combination represents a somewhat complex mode of management with several definite drawbacks. With the advent of the broad-spectrum antibiotics and in vitro evidence of the effectiveness of aureomycin and Chloromycetin against a number of strains of *H. influenzae*, Type B,[9] the possibility of simplifying the treatment of this infection presented itself.

When the present investigation was undertaken in January, 1951, it was not altogether clear whether Chloromycetin without supplemental agents would be effective. Two preliminary reports[10, 11] had been published concerning a total of 22 cases in which Chloromycetin alone had been used. However, these results needed amplification in a larger series of patients before any definitive conclusions were warranted. Hence, it was decided to employ a combination of Chloromycetin and sulfadiazine in a series of consecutive cases until sufficient data could be compiled to allow an assessment of the efficacy of this modality of therapy. Neither streptomycin nor Alexander's rabbit antiserum was used. Since this study was initiated two additional series have been reported[12, 13] in which Chloromycetin had been used alone with excellent results.

Of ancillary interest in the present study was the evaluation of a microcrystalline form of Chloromycetin that could be administered by the intramuscular route. This precluded the necessity of trying to administer the drug by gavage or by rectum to a

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Supported in part by a grant from Parke, Davis and Company, Detroit, Michigan.

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TABLE 1. *Results of Treatment.*

CASE NO.	AGE	RACE	SEX	SYMPTOMS AND SIGNS	DURATION OF ILLNESS BEFORE ADMISSION	PREVIOUS THERAPY	SPINAL-FLUID FINDINGS ON ADMISSION		
							WHITE CELLS	POLYMORPHONUCLEAR LEUKOCYTES	SUGAR
					days		*per cu. mm.*	*%*	*mg./100 cc.*
1	2½ yr.	N	F	Patient critically ill, with convulsions, stupor, some meningeal signs and temperature of 101°F.	2	None	20,000	100	7
2	8 mo.	W	M	Patient acutely ill and lethargic, with bulging fontanelle, meningeal signs, purulent otitis and temperature of 103° F.	2	Penicillin	9,000	98	30
3	4 yr.	W	F	Patient moderately ill, with meningeal signs and temperature of 103°F.	2	Sulfadiazine	175	50	10
4	2 yr.	W	F	Patient acutely ill and stuporous, with meningeal signs and temperature of 103°F.	2	Penicillin	724	30	<10
5	3 yr.	W	F	Patient moderately ill and lethargic, with convulsions, meningeal signs and temperature of 105°F.	4	Penicillin	8,000	96	13
6	1½ yr.	W	F	Patient moderately ill, with meningeal signs and temperature of 103°F.	4	Penicillin	930	87	10
7	1½ yr.	W	F	Patient acutely ill and lethargic, with convulsions, meningeal signs, pneumonia and temperature of 104°F.	7	Penicillin and 750 mg. of terramycin	9,800	89	20
8	2 yr.	W	M	Patient acutely ill and lethargic, with meningeal signs and temperature of 104°F.	2	None	3,400	99	25
9	3½ yr.	W	M	Patient moderately ill, with meningeal signs and temperature of 103°F.	1	None	3,250	95	20
10	15 mo.	W	M	Patient acutely ill and stuporous, with meningeal signs and temperature of 101°F.	2	400 mg. of aureomycin	60,000	97	0
11	2 yr.	N	M	Patient moderately ill, with convulsions, bronchopneumonia, meningeal signs and temperature of 105°F.	2	None	16,900	95	48
12	4 yr.	N	M	Patient acutely ill and lethargic, with meningeal signs and temperature of 103°F.	1	None	2,500	99	—
13	5 mo.	W	M	Patient acutely ill and lethargic, with bulging fontanelle and temperature of 103°F.	2	Penicillin	1,800	83	—
14	2 mo.	W	F	Patient critically ill and lethargic, with bulging fontanelle and temperature of 103°F.	9	None	1,000	95	36
15	1 yr.	W	M	Patient critically ill and comatose, with nystagmus, meningeal signs and temperature of 103°F.	10	Penicillin	1,200	80	16

TABLE 1. (*Concluded.*)

CASE NO.	SPINAL-FLUID FINDINGS ON ADMISSION		CHLOROMYCETIN THERAPY	SULFADIAZINE THERAPY	OTHER THERAPY	DURATION OF FEVER AFTER TREATMENT	PERIOD OF HOSPITALIZATION	RESULT	COMPLICATIONS
	PROTEIN	SMEAR AND CULTURE FOR *H. influenzae*							
	mg./100 cc.					*days*	*days*		
1	210	Positive (Type B)	2 gm. intramuscularly every 12 hr. for 8 days; total of 32 gm.	0.3–0.4 gm. per kg. of body weight every 24 hr. for 8 days	None	2	11	Recovery	None
2	44	Positive (Type B)	1 gm. intramuscularly every 12 hr. for 8 days; total of 16 gm.	0.3–0.4 gm. per kg. of body weight every 24 hr. for 6 days	None	3	16	Recovery	None
3	41	Positive (Type B)	1 gm. intramuscularly every 12 hr. for 3 days; 250 mg. orally every 4 hr. for 7 days; total of 16.5 gm.	0.15–0.3 gm. per kg. of body weight every 24 hr. for 6 days	None	1	12	Recovery	None
4	69	Positive (Type B)	1 gm. intramuscularly every 12 hr. for 5 days; 250 mg. orally every 4 hr. for 5 days; total of 17.5 gm.	0.3 gm. per kg. of body weight every 24 hr. for 5 days	None	1	14	Recovery	None
5	234	Positive (Type B)	1 gm. intramuscularly every 12 hr. for 6 days; total of 12 gm.	0.15–0.3 gm. per kg. of body weight every 24 hr. for 9 days	None	1	11	Recovery	None
6	130	Positive (Type B)	0.5 gm. intramuscularly every 12 hr. for 3 days; 250 mg. orally every 4 hr. for 6 days; total of 12 gm.	0.15–0.3 gm. per kg. of body weight every 24 hr. for 9 days	None	4	14	Recovery	None
7	128	Positive (Type B)	1 gm. intramuscularly every 12 hr. for 9 days; total of 18 gm.	0.3 gm. per kg. of body weight every 24 hr. for 6 days	None	3	10	Recovery	None
8	140	Positive (Type B)	1 gm. intramuscularly every 12 hr. for 4 days; 250 mg. orally every 4 hr. for 4 days; total of 14 gm.	0.3 gm. per kg. of body weight every 24 hr. for 8 days	None	2	10	Recovery	None
9	180	Positive (Type B)	0.5 gm. intramuscularly every 8 hr. for 6 days; 250 mg. orally every 4 hr. for 6 days; total of 18 gm.	0.4 gm. per kg. of body weight every 24 hr. for 12 days	None	3	15	Recovery	None
10	903	Positive (Type B)	1 gm. intramuscularly every 12 hr. for 7 days; total of 14 gm.	0.3 gm. per kg. of body weight every 24 hr. for 7 days.	None	3	13	Recovery	Transitory weakness of lower extremities
11	150	Positive (Type B)	1 gm. intramuscularly every 12 hr. for 3 days; 250 mg. orally every 6 hr. for 6 days; total of 12 gm.	0.4 gm. per kg. of body weight every 24 hr. for 7 days	None	3	13	Recovery	Black tongue and measles
12	—	Positive (Type B)	0.8 gm. intramuscularly every 8 hr. for 3 days; 500 mg. orally every 6 hr. for 7 days; total of 25 gm.	0.3 gm. per kg. of body weight every 24 hr. for 3 days	None	5	14	Recovery	None
13	—	Positive (Type B)	1 gm. intramuscularly every 12 hr. for 10 days; total of 20 gm.	0.3 gm. per kg. of body weight every 24 hr. for 5 days	None	1	56	Recovery	Subdural effusion; bilateral membranes (removed at craniotomy).
14	85	Positive (Type B)	1 gm. intramuscularly every 12 hr. for 1 day; total of 2 gm.	None	Antiserum and aureomycin	—	—	Death 26 hr. after admission	—
15	200	Positive (Type B)	1 gm. intramuscularly every 12 hr. for 21 days; total of 42 gm.	0.3 gm. per kg. of body weight every 24 hr. for 4 days	Antiserum, streptomycin and terramycin	—	—	Death	—

comatose patient during the acute phase of the disease.

Clinical Features

The present series consisted of 15 consecutive cases of meningitis due to *H. influenzae* admitted to the Children's Hospital from January, 1951, to February, 1952. The ages of the patients ranged between two months and four years, with a mean of two and one-tenth years. Four of the patients were less than one year of age. There were 8 males and 7 females, 3 being Negroes and 12 whites.

The degree of illness on admission varied in the 15 patients. Three were regarded as critically, 7 as acutely, and the remaining 5 as moderately ill. The temperature varied from 101 to 105°F. at the time of hospitalization. Two patients had a complicating bronchopneumonia, and another had a purulent otitis media.

The duration of illness prior to admission ranged from one to ten days, with an average of two and five-tenths days. Of the 15 patients, 7 had had no therapy prior to admission, 5 had been treated with penicillin for one or two days, 1 had received sulfadiazine for two days, 1 had been given four 100-mg. doses of aureomycin, and still another had received three 250-mg. doses of terramycin before hospitalization.

Laboratory Aspects

Bacteriologic examination of the spinal fluid obtained on initial lumbar puncture showed *H. influenzae* in all cases. The spinal-fluid white-cell count ranged from 125 to 60,000 per cubic millimeter, with a predominance of neutrophils ranging from 83 to 100 per cent. The white-cell count in the spinal fluid was above 500 in all cases but 1. Positive blood cultures on admission were obtained in 10 of the 15 patients.

Mode of Therapy

All 15 patients received a combination of Chloromycetin and sulfadiazine.

Chloromycetin was administered intramuscularly initially because of the simplicity afforded by the parenteral route in an acutely ill child. Oral medication in a semicomatose or refractory child with meningitis is most difficult or impossible, and the desirability of parenteral administration becomes manifest. This is especially true of the broad-spectrum antibiotics the unpleasant taste of which, until recently, was an important consideration. Recently, a finely divided microcrystalline form of Chloromycetin has been made available for experimental purposes. When diluted with physiologic saline solution, a suspension results that can readily be administered with a syringe and can be injected intramuscularly. Prior to its use in this series, a preliminary study was made to determine the nature of the blood levels obtained when the suspension was administered to a group of normal children with the dosage predicated on a weight basis. These results will be reported at length in a forthcoming paper.[14] Briefly, it was found that in children under two years of age, a dose of microcrystalline Chloromycetin suspension ranging between 100 and 150 mg. per kilogram of body weight produces adequate therapeutic blood levels for twenty-four hours or longer after a single injection intramuscularly. This was the dose employed in the present series. Toxic effects from intramuscular injection of Chloromycetin were confined to local tissue reactions in the buttocks that sometimes followed four or five consecutive injections. Intramuscular administration of Chloromycetin proved to be a simple and effective mode of therapy in a series of over 200 patients (including cases of pneumonia, typhoid fever, pertussis, laryngotracheobronchitis and peritonitis) treated at the Children's Hospital during the past eighteen months.

In the present series, intramuscular injection of Chloromycetin was discontinued as soon as feasible, and Chloromycetin by mouth was initiated in a dose of 100 to 150 mg. per kilogram of body weight per day in a four-hour to six-hour divided dosage schedule. In the early portion of this study, crystalline Chloromycetin was employed as the oral preparation; however, more recently, Chloromycetin palmitate, a palmitic acid ester of chloramphenicol, has been used instead because of its palatability and ease of administration to children.[15]

In addition to Chloromycetin, sulfadiazine was given to all 15 patients in the present series. The average dose was 0.30 to 0.4 gm. per kilogram of body weight every twenty-four hours during the acute phase and 0.15 to 0.30 gm. during the convalescent period. Usually, the drug was administered parenterally (either intravenously or subcutaneously) at the time of admission in an eight-hour divided dosage schedule, and the oral route was adopted as soon as the condition of the patient permitted. An attempt was made to achieve blood sulfadiazine levels ranging between 10 and 15 mg. per 100 cc. during the acute phase of the disease.

Two patients (both of whom died subsequently) received additional therapy because they were desperately ill on admission to the hospital. In 1, rabbit antiserum and aureomycin were administered; the other received rabbit antiserum, streptomycin and terramycin in addition to Chloromycetin and sulfadiazine.

Results

In 15 consecutive cases in which treatment consisted of combined Chloromycetin and sulfadiazine, 13 patients recovered, and 2 died (Table 1).

In the 13 patients who recovered, the duration of fever after treatment was initiated ranged from one to eight days. Ten patients showed a defervescence to normal within three days or less, and

the duration of temperature elevation in the remaining three cases was four, five and eight days respectively. The average duration of fever after therapy was started was two and eight-tenths days. Similarly, there was a general clinical improvement characterized by clearing of sensorium and subsidence of meningeal signs two to five days after therapy was begun. Coinciding with the clinical improvement was a prompt disappearance of the organisms from the spinal fluid, usually within twenty-four to forty-eight hours. There was generally a sharp decrease in pleocytosis and a return to normal of spinal-fluid sugar and protein within three to six days of the initiation of therapy.

The duration of therapy varied; Chloromycetin was administered intramuscularly for periods ranging from three to twenty-one days, with an average of six days. In 7 of the 15 patients, the intramuscular route was the only method of administration employed. However, in the remaining 8 cases, the oral route was adopted after an initial trial with intramuscular administration. The average total duration of Chloromycetin therapy (including the intramuscular and oral routes) was nine and five-tenths days. The total amount of Chloromycetin varied from 12 to 42 gm. in 14 patients, with an average of 18.1 gm. per patient; 1 baby was given the drug for only one day in a dose of 2 gm. before death ensued.

The duration of sulfadiazine therapy ranged from three to twelve days, with an average of seven days per patient.

The length of hospitalization in the present series ranged from ten to fifty-six days. Of the 13 patients who recovered, 11 were discharged within sixteen days; 1 developed measles on the ward and his hospitalization was prolonged to twenty-seven days; and 1 developed bilateral subdural effusions, requiring a craniotomy, and remained in the hospital for fifty-six days.

Fatal Cases

The 2 patients who died in this series are worthy of further comment.

The first death (Case 14) occurred in a two-month-old female infant who was admitted to the hospital critically ill. She was markedly lethargic and had a bulging fontanelle. This infant had been ill for nine days prior to admission. The spinal-fluid examination on admission showed 1000 white cells per cubic millimeter, with 95 per cent neutrophils. Smear and culture of the spinal fluid were positive for *H. influenzae*, Type B, organisms. She received rabbit antiserum, aureomycin and adrenocortical extract during the first twenty-four hours after admission. Her condition rapidly deteriorated and on the second day after entry, 1 gm. of Chloromycetin at twelve-hour intervals was administered intramuscularly. The infant died within thirty-six hours of admission.

A second death (Case 15) occurred in a one-year-old boy, who was admitted to the hospital in a comatose state with a temperature of 103°F. Nystagmus and meningeal signs were observed on admission. The child had been ill for ten days prior to entry and had been treated with penicillin before hospitalization. The initial spinal fluid contained 12,000 white cells per cubic millimeter, with 80 per cent neutrophils and a sugar of 16 mg. and a protein of 200 mg. per 100 cc. Smear and culture of the spinal fluid revealed numerous *H. influenzae*, Type B, organisms. Shortly after admission, the child became spastic and opisthotonic, and on the fourth day, a craniotomy was performed, 60 cc. of purulent material being evacuated from the left subdural space. Four days later, he was again operated upon, and plastic adhesions were found over the entire cortex. Therapy in this case consisted of Chloromycetin, sulfadiazine, rabbit antiserum, streptomycin and terramycin. The patient died twenty-eight days after admission to the hospital.

Thus, both fatal cases occurred in patients who had been ill for nine and ten days respectively before admission. These cases emphasize again the fact that no matter how effective a therapeutic agent may be, early diagnosis and early initiation of therapy (especially in children under one year of age) are of paramount importance.

Complications

Of the 13 children who recovered, 1 had complications referable to meningitis. This patient (Case 10) showed some transitory weakness of the lower extremities at the time of discharge.

In spite of the large doses of Chloromycetin and sulfadiazine employed in this series, there was no discernible toxic effect referable to the hematopoietic system.

The most frequent untoward effect encountered was moderate local reaction of the tissues in the buttocks after four to six days of intramuscular injection of Chloromycetin. Varying degrees of local pain, tenderness and induration were observed. When the intramuscular route was discontinued within three or four days and the oral mode of administration adopted, considerably less local irritation was encountered. Local reactions were more frequent in the very young patients, in whom less muscle tissue was present.

Case Report

The following case serves to illustrate the course and management of a representative case of *Haemophilus influenzae* meningitis in the present study.

Case 1. M. G., a 2½-year-old Negro girl, was admitted to the hospital on January 15, 1951, with the presenting symptoms of fever and drowsiness. Two weeks prior to admission, a mild respiratory infection with a nonproductive cough had developed. She received a dose of 300,000 units of procaine penicillin intramuscularly at that time, with some apparent improvement. She remained afebrile during the

next 2 weeks until the night before admission, when she awoke with a high temperature and had a convulsive seizure. Hospitalization was advised.

Physical examination showed an acutely ill child with a temperature of 102°F. A moderate degree of nuchal rigidity was elicited. Kernig and Brudzinski signs were negative. Physical examination was otherwise not remarkable.

A spinal tap performed shortly after admission yielded cloudy fluid that contained 20,000 white cells per cubic millimeter, of which 100 per cent were neutrophils. A gram-stained smear revealed a few pleomorphic bacilli, which were identified as *H. influenzae*, Type B. The spinal-fluid sugar was 7 mg., and the protein 210 mg. per 100 cc. Blood and spinal-fluid cultures grew out *H. influenzae*, Type B.

The patient received Chloromycetin intramuscularly in a dose of 2 gm. every 12 hours. In addition, sodium sulfadiazine in a dose of 0.3 gm. per kilogram of body weight was given subcutaneously in an 8-hour divided dosage schedule.

Within 24 hours of admission the child appeared much improved and showed a considerable clearing of her sensorium. The temperature fell to normal within 2½ days, and the patient remained afebrile during the remainder of her hospital course. Lumbar puncture repeated 2 days after admission revealed 1160 white cells per cubic millimeter, with 90 per cent neutrophils. Smear and culture of the spinal fluid at that time disclosed no organisms. A third spinal tap performed 4 days later showed 33 white cells per cubic millimeter, with normal sugar and protein.

Therapy was discontinued after 8 days, and the patient was discharged on the 11th hospital day after an uneventful recovery. No neurologic sequelae were observed.

Discussion

In the present series, the use of combined Chloromycetin and sulfadiazine appeared to be an effective mode of therapy. As a rule, the temperature rapidly came down to normal and *H. influenzae* promptly disappeared from the spinal fluid. Similarly, there was generally a sharp decrease in pleocytosis and a prompt return to normal of spinal-fluid sugar and protein within three to six days of the initiation of therapy. The rapidity of recovery in these cases surpasses that produced by any other type of therapy previously employed at this hospital.

The complex therapeutic regime that had been employed until the recent advent of broad-spectrum antibiotics usually included the administration of streptomycin intramuscularly and intrathecally, together with sulfadiazine and Alexander's rabbit antiserum. Alexander et al.[4] recommended this vigorous therapeutic approach in moderately and severely ill patients. In a series of 25 patients, complete recovery occurred in 76 per cent, recovery with residua in 12 per cent, and death in 12 per cent. In a recent series reported by Crook and his associates[16] 49 patients with meningitis due to *H. influenzae* were treated with this triple combination of drugs. A complete recovery was observed in 65 per cent and recovery with residua in 19 per cent, with a mortality of 16 per cent. However, some objections to the use of streptomycin and antiserum do exist and can be given as follows:

Streptomycin

May have a toxic effect on the eighth nerve, with vestibular derangement and deafness after prolonged therapy.[17]

Allows the occasional development of resistant strains of organisms.

Traverses the blood-brain barrier poorly after intramuscular administration and hence concomitant daily intrathecal injection of the drug is recommended.[18] However, Hoyne and Brown[19] have recently interdicted the intrathecal administration of streptomycin as being both unnecessary and hazardous and concluded that equally good results can be obtained with intramuscular administration alone.

Rabbit Antiserum

May produce delayed serum reactions characterized by fever, urticaria and swollen joints in approximately 20 per cent of cases.

Increases excessively the cost of treatment to the hospital or patient. The requirements for adequate therapy range between 8 and 10 vials per patient, at a cost of approximately $30 per vial. Thus, adequate antiserum therapy would cost $240 to $300 per patient.

The question whether or not streptomycin and rabbit antiserum can be safely omitted from the therapeutic regimen since the advent of Chloromycetin is an important one. It is probably too early to make a categorical statement, and additional series of cases will be required before comparison with other modalities of therapy can be safely made. However, the data accumulated thus far — both from our results and from the reports of Prather and Smith,[11] McCrumb et al.,[12] Carabelle and his associates[10] and Schoenbach et al.[13] — indicate that Chloromycetin is an extremely effective agent in treatment. The in vitro sensitivity of *H. influenzae* in 10 case strains has been reported to range between 0.4 and 5 microgm. per cubic centimeter.[12] These sensitivities are well within the range of concentrations that can be achieved and maintained by therapeutic doses of Chloromycetin given either orally or intramuscularly. It is well to mention that when Chloromycetin is employed in these cases no concomitant intrathecal administration of the drug is required since it has been demonstrated that this drug traverses the blood-brain barrier adequately, 30 to 50 per cent of the co-existing blood level of the drug appearing in the spinal fluid.[20]

Whether a sulfadiazine-Chloromycetin combination offers an advantage over Chloromycetin alone remains to be seen. The antibacterial effect of sulfadiazine against *H. influenzae*, Type B, has been confirmed by several investigators,[21, 22] and there are no cogent deterrents to the use of sulfadiazine comparable with those previously outlined for streptomycin and rabbit antiserum. Sulfadiazine can be administered inexpensively and easily and with very little hazard to the patient. However, our results in 15 patients treated with a combination of sulfadiazine and Chloromycetin were no

better than those observed by others after the use of Chloromycetin alone. A total of 46 cases in which the patients were treated with Chloromycetin alone have been reported thus far, with no deaths.[10-13] Moreover, the incidence of neurologic sequelae was remarkably low. This shows that Chloromycetin is effective without additional therapy in mild to moderate cases. In severe cases, on the other hand, there may yet be found some advantage to the combined use of Chloromycetin and sulfadiazine. Further observations are needed to settle this point.

The administration of Chloromycetin intramuscularly was indicated during the initial phase of the disease. During this period when the child was acutely ill and often semicomatose, the intramuscular route contributed to the simplification of management, precluding necessity of gavage feeding or rectal instillation of the drug. Moreover, the demonstration that therapeutic blood levels of Chloromycetin may still be present for twenty-four hours after the injection of a single intramuscular dose of 100 to 150 mg. of microcrystalline Chloromycetin suspension per kilogram of body weight makes it possible to give the drug only once or twice per day. Substitution of oral for intramuscular administration of Chloromycetin within three or four days diminishes substantially the incidence of local tissue reactions in the buttocks.

Summary and Conclusions

Fifteen infants and children with meningitis due to *Haemophilus influenzae* were treated with combined sulfadiazine and Chloromycetin therapy. Of this number, 13 recovered and 2 died. The 2 deaths occurred in infants two and twelve months of age who had been ill for nine and ten days, respectively, prior to hospital admission. One patient who recovered showed some transitory weakness of the lower extremities.

Chloromycetin was administered intramuscularly in the form of a fine microcrystalline suspension during the acute phase of the disease. Preliminary absorption studies in a series of normal children indicated that, in those under two years of age, a single intramuscular injection of Chloromycetin suspension in a dose ranging from 100 to 150 mg. per kilogram of body weight will produce adequate therapeutic blood titers for twenty-four hours or longer.

A simple and effective mode of therapy is the intramuscular injection of Chloromycetin in a dose of 100 to 150 mg. per kilogram of body weight at intervals of twelve to twenty-four hours during the first three or four days after admission, followed by a subsequent change to oral administration after the acute phase has subsided. A palatable oral preparation such as Chloromycetin palmitate is recommended in a dose of 100 to 150 mg. per kilogram, a four-hour to six-hour divided dosage schedule being preferred. Therapy should be maintained for approximately ten days or longer. Hematologic studies should be done frequently during the course of Chloromycetin administration.

The desirability for the simultaneous administration of sulfadiazine requires further investigation.

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METABOLIC STUDIES FOLLOWING TOTAL PANCREATECTOMY FOR RETROPERITONEAL LEIOMYOSARCOMA

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BOSTON

TOTAL pancreatectomy has been reported 27 times (June, 1952).[1-20] In all cases this procedure was done to remove intrinsic pancreatic disease. In the case reported below, total pancreatectomy was part of an attempted excision of a large retroperitoneal sarcoma invading the pancreas and splenic vein. The patient survived one year. The metabolic studies carried out during this period form the substance of this report.

CASE REPORT[21]

S. K., a 33-year-old electrician, entered the hospital on June 22, 1950, because of a left-upper-quadrant mass of 2 weeks' duration.

The patient had complained of vague, intermittent, left-costal, and costovertebral-angle distress for 2 years. Two weeks prior to admission he had discovered a mass in the upper abdomen. He was otherwise asymptomatic.

Physical examination showed an apparently healthy, well developed man, with a firm, nontender, nonmovable mass filling the entire left upper quadrant. Enlarged lymph nodes were present in both axillas. Examination was otherwise negative.

Examinations of the blood and urine and liver-function studies were negative. X-ray films revealed a large left-upper-quadrant mass displacing the stomach anteriorly and the splenic flexure inferiorly. No esophageal varices were seen.

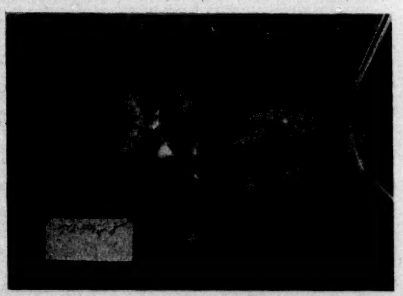

FIGURE 1. *Specimen Removed at Operation, Showing Tumor Thrombus Extending into the Splenic Vein.*

On July 13, exploration was carried out through a left thoracoabdominal incision. The preoperative diagnosis was splenic cyst. The spleen was found to be normal, sitting astride a large retroperitoneal mass that had invaded the tail of the pancreas. Frozen sections confirmed the suspicion of carcinoma. A block resection of the mass, including the spleen, body and tail of the pancreas, was carried out. It was then noted that tumor thrombus had extended into the splenic vein at the point of its division (Fig. 1). Frozen sections showed tumor in the remaining pancreatic stump. Resection of the duodenum and head of the pancreas was then carried out, continuity being re-established by means of an end-to-end cholecystjejunostomy, end-to-side choledochojejunostomy and retrocolic gastrojejunostomy.

The pathological diagnosis was retroperitoneal leiomyosarcoma, with extension into the pancreas and spleen and invasion of the splenic vein.

The patient did well postoperatively and was discharged home on the 28th day after operation. He survived for 1 year. Autopsy showed recurrent retroperitoneal leiomyosarcoma, with metastases to the liver, stomach and mesenteric lymph nodes.

METABOLIC STUDIES

The patient's over-all metabolic course during the year he survived is summarized in Figure 2. Detailed studies are outlined below.

Insulin

The patient's eventual insulin requirements were only 10 units each of protamine zinc and crystalline insulin. This is similar to the low requirements previously reported. In 1 case insulin was never found necessary, and the patient was living and well sixteen months after total pancreatectomy.[18] The possibility of ectopic pancreatic tissue affords an explanation for this finding.[22] In 3 cases diabetes existed before operation; after total pancreatectomy the severity of the disease did not appreciably increase in 1 case, and increased only slightly in the other 2 patients.[4, 8, 11] Thorogood and Zimmermann[23] have carried out some experiments that may help to explain these paradoxical findings. They found that pancreatectomy reduced the insulin requirements of alloxan-diabetic animals and postulated the presence of a diabetogenic factor in the pancreas.

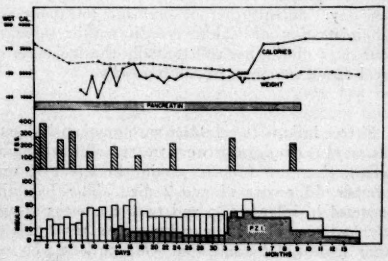

FIGURE 2. *Metabolic Status during the Year the Patient Lived after Operation.*

Fatty Livers

Pancreatectomized dogs maintained on standard diets develop fatty infiltration of the liver unless

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lipotrophic agents are supplied. In all reported cases of pancreatectomy in human beings, this liver change has not been found. The case reported above was no exception.

It is probable that the diet of man is adequate in lipotrophic factors to prevent the fatty changes noted in dogs.[6, 10]

Phospholipid Metabolism

No study of phospholipids in a pancreatectomized patient has previously been reported. Barker et al.[24] fed normal and pancreatectomized animals radioactive phosphorus and sampled the phosphorus activity in the plasma phospholipid at varying intervals. They showed a reduced ability of the pancreatectomized animals to incorporate recently ingested radiophosphorus into phospholipid. This they assumed to be hepatic in origin and related to the absence of the pancreas. The development of fatty livers in their animals was postulated as being related to the inability of the phosphorylation mechanisms to handle the neutral triglyceride brought to it.

In view of the failure of fatty livers to develop in human patients, it was considered of interest to repeat the experiment of Barker et al. on the human being.

The patient described above was readmitted to the hospital for study six months after operation. At that time the diabetes was well regulated, and the diet and weight were constant. Radioactive phosphorus was administered intravenously, and the activity in plasma phospholipid determined at varying times.

Another patient of the same age who was apparently well, except for a tumor of the thigh, was treated identically and used as a control.

The time-rate relations of the curves were quite similar (Fig. 3). These findings, in a sense, support those of Barker et al., for, if development of fatty livers in dogs is in part due to faulty phosphorylation, as expressed by the difference in their curves, the absence of such marked differences in the experiment summarized in Figure 3 may help explain the absence of these findings in clinical material.

Stools

While the patient was in the hospital for study pancreatin was omitted from his diet. Thereafter, he refused to take it, claiming that the untoward gastric symptoms did not warrant the slight improvement in consistence and frequency of stools that resulted. The improvement in appetite and caloric intake after pancreatin had been discontinued was strikingly demonstrated in the metabolic chart (Fig. 2). This is in accord with the experience of Phemister.[25] Stool analysis in the absence of pancreatin revealed only 22 per cent fat. Whipple[9] found that 3 out of 5 patients subjected to radical pancreatectomy showed no stool disturbances. In a discussion of this paper Brunschwig reported a case of total pancreatectomy and total gastrectomy in which the patient showed no changes in the character of the stools.

Although pancreatin and similar supplements frequently increase the efficiency of fat and nitrogen absorption in pancreatectomized patients, the findings discussed above suggest that such supplements are not always necessary and may sometimes be detrimental by affecting the patient's appetite and caloric intake. The possible supplementary role of the succus entericus must also be considered.

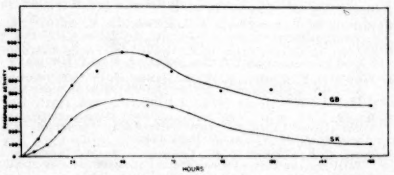

FIGURE 3. *Plasma Phospholipids after Administration of Radioactive Phosphorus in a Pancreatectomized Patient (S. K.) and in a Control (G. B.).*

Amylase and Lipase

Normal serum amylase and lipase have been found long after total pancreatectomy in all cases reported except 1.[18] This was the same patient who required no insulin.

In the case reported above, amylase and lipase were repeatedly found to be present and normal in value.

Blood Clotting

Multiple venous thrombi appear to occur more often in carcinoma of the pancreas than in carcinoma of other organs. This is particularly true of carcinoma of the body and tail.[26, 27] Thrombophlebitis was observed in 28 per cent of 100 autopsied cases of carcinoma of the pancreas.[27] These abnormalities of blood clotting may be related to circulating trypsin secondary to neoplastic obstruction.[27-31] This increased clotting tendency has not been observed in patients subjected to radical resection. Complete blood studies, including clotting and bleeding time, osmotic fragility and prothrombin time, were normal in the case reported above before and after operation.

SUMMARY

Total pancreatectomy was carried out as part of a radical excision of a retroperitoneal leiomyosarcoma. The patient survived for one year. The "brittle" type of diabetes developed and required only 20 units of insulin daily.

There was no fatty infiltration of the liver. Radioactive phospholipid studies suggest that absence of

the pancreas in man does not result in abnormalities of phospholipid metabolism as reported in dogs.

The patient's nutritional status was better without pancreatin than with it.

Serum amylase and lipase were repeatedly present in normal concentrations after total pancreatectomy.

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SUSCEPTIBILITY TO DIPHTHERIA AMONG ELDERLY PERSONS*
Immunization by the Intracutaneous Administration of Toxoid

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THIS study attempts to evaluate the incidence of susceptibility to diphtheria and the sensitivity to diphtheria toxoid among elderly persons. In addition, a pilot study on a method of immunizing susceptible elderly people is described.

Diphtheria is ordinarily considered a disease of childhood, and thirty years ago the great majority of cases did occur in the first few years of life. According to Schick,[1] 67 per cent of cases occurred between the ages of two and six years, and diphtheria was "rarely observed in adult life." Similarly, Top[2] stated that 80 per cent of cases occurred before the age of ten years. In Denmark, before World War II, the ratio of adult to childhood cases of diphtheria was 1:3.[3]

In the intervening years vigorous campaigns for the protection of children against diphtheria have become increasingly effective, so that at present the great majority of children in urban areas have received artificial immunization.[4] Consequently, diphtheria has become an uncommon infection in childhood, and the incidence of the disease at large has declined. As a result of this decreased incidence, the opportunity to acquire or maintain natural immunity by means of exposure to *Corynebacterium diphtheriae* presumably has also been reduced.

During the past six years the incidence of diphtheria has increased sharply in San Francisco. At the same time, the average age of patients who contract the disease has also increased dramatically, so that at present approximately 60 per cent of such patients are over thirty years old.[5] In addition, the complications and mortality are at a maximum among elderly persons.[5] In Denmark the incidence of diphtheria has also increased; and in 1945 the ratio of adult patients to children was 2.8:1.[3]

Whereas Schick[1] originally observed only 14 per cent of persons over the age of seventeen years who were Schick-positive reactors, recent surveys have reported an increase in the incidence of susceptibility to diphtheria among adults. In more than

*Presented at the annual meeting of the Western Society for Clinical Research, Seattle, Washington, January, 1951.

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4000 American servicemen tested during World War II, Schulze[6] found that 29.7 per cent were Schick positive and that the incidence of the Schick-positive state increased with age. Similarly, Cheever,[7] in a study of 18,000 Navy recruits, found that the percentage of Schick-positive reactors increased with age. Although only 27 per cent of the men were positive reactors at seventeen years of age, the incidence gradually increased to 45 per cent at 26 years of age. Karelitz and Moloshok[8] found that 28.6 per cent of 1283 soldiers gave positive reactions to Schick tests. In San Francisco 23.6 per cent of 636 high-school students tested in 1948 gave Schick-positive reactions.[4]

The artificial immunization of adults to diphtheria by the methods used for children has never been feasible on a large scale because of the high incidence of untoward reactions to the immunizing material, general or severe local reactions being reported in 10 to 30 per cent given toxoid by the subcutaneous route.[9-11] Although satisfactory immunity has been reported to result from a reduced dose of 0.2 cc. administered subcutaneously, the incidence of systemic reactions remained almost as high as that after injection of 0.5 or 1.0 cc. of toxoid.[3]

The Moloney test for sensitivity to toxoid[12] has been widely used to determine which subjects are likely to manifest unpleasant reactions. The test consists of the intradermal injection of 0.1 cc. of toxoid diluted 1:10 to 1:100 (usually 1:20). A positive reaction is manifested by an area of redness or induration, 1 cm. or more in diameter, 48 hours after injection. It has been observed that systemic reactions to immunization occurred more frequently in Moloney-positive than in Moloney-negative persons. Furthermore, most observers have found the incidence of positive Moloney reactions to be greater with increasing age.[11, 13, 14] Scheibel and his associates,[9] on the other hand, found no increase in the Moloney-positive state with advancing age among subjects under fifty years old and noted a decline in toxoid sensitivity beyond this age.

Attempts at immunization with a variety of antigens administered intradermally have been successful. In 1931 Tuft[15] reported active immunization against typhoid with antigen given by this route. Similarly, protection against scarlet fever[16] and influenza[17, 18] has been accomplished. In 1933 Goldbloom and Klein[19] were able to immunize children against diphtheria by the use of concentrated toxoid injected intradermally. Kern et al.[20] succeeded in immunizing allergic and nonallergic children and young adults by use of a single intradermal injection of alum-precipitated diphtheria toxoid, and found the reaction rate to be lower than that after administration by the subcutaneous route. Bunch and his associates[14] successfully immunized medical and nursing students, whose Moloney reactions were positive, by intracutaneous injections at weekly intervals. Subjects with weakly positive Moloney reactions received individual doses of 0.1 cc. of a 1:10 dilution of toxoid, whereas those with strongly positive Moloney reactions received doses of 0.1 cc. of a 1:100 dilution. No general or severe local reactions were observed.

Materials and Methods

Subjects for this investigation were 171 ambulatory volunteers from a home for the aged.* The age range was forty-seven to eighty-six years.

Initially, each subject received intradermal injections on the forearm of 0.1 cc. of Schick toxin, 0.1 cc. of heated Schick toxin as a control, and 0.1 cc. of a 1:20 saline dilution of alcohol-fractionated diphtheria toxoid.† The skin tests were read on the second and seventh days after administration and were interpreted according to the usual, accepted criteria. In addition, blood samples for diphtheria antitoxin determination were obtained on the second day on all subjects whose reactions to the Schick test appeared to be early positive. The few remaining Schick-positive persons were bled for antitoxin titers on the seventh day. Thus, most initial antitoxin titers could not have been the result of stimulation by the materials used in the Schick and Moloney tests.

Thirty-six Schick-positive persons from the previously determined susceptible group were then given an intracutaneous injection of alcohol-fractionated diphtheria toxoid at monthly intervals for three months. This group was arbitrarily divided into two sections, each of which included both Moloney-positive and Moloney-negative reactors. The first section, composed of 23 subjects, received an injection of 0.1 cc. of undiluted toxin once a month for three months. The second section, of 13 subjects, received an injection of 0.1 cc. of a 1:10 saline dilution of toxoid on three occasions at monthly intervals. The subjects were instructed to report to the dispensary if they felt ill after an injection; in addition, they were questioned about reactions at the time of the next injection. Routine temperature recordings were not taken.

At the time of the third injection, two months after the initial injection, 18 persons selected at random were bled for diphtheria antitoxin determination. Three months after the third toxoid injection, the remainder were bled for antitoxin titer, and the entire group was retested with Schick toxin and heated toxin control. The Schick reaction was selected as the final criterion of immunity since antitoxin determinations were performed on random samples of persons at two different intervals after immunization, rather than on the whole group simultaneously. Serum antitoxin titers were deter-

*Facilities for this study at the Laguna Honda Home were furnished through the co-operation of Dr. H. D. Crail and Dr. J. C. Geiger.

†The diphtheria toxoid used in this study was kindly furnished by the Eli Lilly Company.

mined according to the method of Kellogg,[21] using adult white guinea pigs. The tests were performed to determine antitoxin titers of 0.033 unit per cubic centimeter or higher and 0.016 unit per cubic centimeter or less.

Discrepancies in the numbers of Moloney and Schick readings are due to the fact that some subjects did not report on the second day when the Moloney reactions were interpreted and others did not report on the seventh day when the Schick reactions were interpreted. Eight subjects who did not complete the course of immunization for reasons not connected with the experiment were discarded from the series. Six on whom final antitoxin determinations were made did not report for the final Schick reading.

TABLE 1. *Schick and Moloney Reactions in Elderly Persons.*

REACTION	SCHICK	MOLONEY
Positive	44 (26.7%)	95 (58.3%)
Negative	121 (73.3%)	68 (41.7%)
Totals	165	163

RESULTS

In 165 interpretable Schick tests, 44 subjects gave positive results, and 121 negative results. Of 163 Moloney reactions, 95 were positive and 68 were negative (Table 1). Of the 44 Schick-positive subjects, 34 had less than 0.016 unit of antitoxin per cubic centimeter of serum, 8 had 0.016 unit, and 2 had 0.033 unit or more. Antitoxin determinations were performed on the serum of only 9 Schick-negative subjects, but in 2 of these the titer was less than 0.016 unit per cubic centimeter.

Of 18 antitoxin determinations performed a month after the second injection of toxoid, 14 demonstrated a titer of 0.016 unit per cubic centimeter or greater, whereas all but 4 subjects had had titers under this level before immunization (Table 2). Antitoxin determinations performed on the serums of the remaining 18 persons in the group three months after the third injection of toxoid showed that 11 subjects had titers of 0.016 unit per cubic centimeter or greater. The observation that 14 of 18 persons had antitoxin titers in excess of 0.016 unit per cubic centimeter a month after the first injection, as compared with only 11 of 18 persons three months after the third injection, may be accounted for by the fact that more Moloney-positive persons were included in the first random sample. Since both samples were small, it is believed that this does not represent rapid loss of immunity. No subject had an antitoxin titer of 0.033 unit per cubic centimeter or greater before immunization, but such titers developed in 23 during or after immunization. Two of 11 persons whose antitoxin titers remained less than 0.016 unit per cubic centimeter became Schick negative after immunization, whereas 1 subject whose final antitoxin titer was over 0.033 unit per cubic centimeter remained Schick positive.

Of 30 Schick tests performed three months after the third injection of toxoid, 21 were negative and 9 were positive (Table 3). All of 9 Moloney-positive subjects became Schick negative, regardless of which dose of toxoid had been used. Of the 9 subjects who remained Schick positive, 7 were Moloney negative, and 2 had an unknown Moloney status.

Six untoward reactions after injection of toxoid were noted by 4 subjects, all of whom were Moloney positive. Two reactions consisted of mild constitutional symptoms, and the remainder were painful local reactions at the site of injection. No reaction was sufficiently severe to preclude completion of the prescribed course of immunization.

TABLE 2. *Diphtheria Antitoxin Titers before, during and after Immunization.*

TITER	BEFORE IMMUNIZATION	SAMPLE NO. 1*	BEFORE IMMUNIZATION	SAMPLE NO. 2†	BEFORE IMMUNIZATION	BOTH SAMPLES
unit per cc. of serum	NO. OF SUBJECTS	NO. OF SUBJECTS	NO. OF SUBJECTS	NO. OF SUBJECTS	NO. OF SUBJECTS	NO. OF SUBJECTS
<0.016	14	4	14	7	28	11
0.016	4	1	4	1	8	2
>0.033	0	13	0	10	0	23

*Subjects bled one month after two toxoid injections.
†Subjects bled three months after three toxoid injections.

DISCUSSION

The incidence of the Schick-positive state among elderly persons is slightly greater than that among children and adolescents in San Francisco. This relatively high level of apparent susceptibility, in

TABLE 3. *Schick Reactions after Immunization according to Status of Moloney Reaction.*

INITIAL MOLONEY REACTION	FINAL SCHICK REACTION	
	NO. POSITIVE	NO. NEGATIVE
Positive	0	9
Negative	7	12
Unknown	2	0
Totals	9	21

addition to the possibility of increased likelihood of exposure to diphtheria, may account for the prevalence of the disease in this age group. Discrepancies have been described between the Schick status and serum antitoxin concentration.[12] The amount of circulating antitoxin necessary to produce immunity may be less than that required to produce Schick negativity. On the other hand, diphtheria may occur in persons who are Schick negative and who demonstrate a high serum antitoxin concentration.[5, 21] For survey purposes, however, the Schick reaction may be considered a valid index of susceptibility to diphtheria.

The Schick level of immunity was formerly thought to be at 0.033 unit of antitoxin per cubic centimeter of serum.[21] More recently, 0.01 unit of antitoxin per cubic centimeter has come to be considered a closer approximation.[22, 23] Our data suggest that the latter estimate is more nearly correct in Schick-positive subjects. Our data on Schick-negative persons are too meager for analysis, but 2 of 9 such subjects had less than 0.016 unit of antitoxin per cubic centimeter of serum. After immunization, the increase of antitoxin titer closely paralleled the Schick reaction. Of 9 persons who remained Schick positive, only 1 showed an increase in antitoxin titer to more than 0.016 unit per cubic centimeter.

A positive reaction to the Moloney test indicates sensitivity to diphtheria toxoid and may be used to predict untoward reactions during prophylactic administration of toxoid.[12] The high incidence of sensitivity to toxoid among older persons thus supports the observation that untoward reactions to immunization are common in adults. On the other hand, such sensitivity to toxoid is most likely a result of previous exposure to *C. diphtheriae* and might indicate some degree of immunity. This supposition is borne out by the fact that more Moloney-positive persons are Schick negative (83.3 per cent) than are Schick positive (16.7 per cent) (Table 4). Furthermore, as suggested by Pappenheimer and Lawrence,[24-26] such partially immune persons might be more easily immunized than those in whom no basic immunity existed. The high percentage of Schick conversion in Moloney-positive subjects by the intradermal injection of toxoid, as contrasted to the relatively low rate of conversion in the Moloney-negative group, appears to confirm this hypothesis. On the basis of this pilot study, it seems that the intradermal route provides an effective means for immunizing Moloney-positive persons without causing serious untoward reactions. On the other hand, the intradermal injection of small amounts of toxoid in Moloney-negative subjects does not produce sufficient reversal of Schick reactions to be justified. Whether undiluted toxoid or toxoid diluted 1:10 was used did not appear to affect the results. Further studies on larger numbers of susceptible persons are desirable to confirm this opinion.

Summary and Conclusions

Positive Schick reactions occurred in 26.7 per cent of 165 elderly subjects.

Positive Moloney reactions occurred in 58.3 per cent of 163 elderly persons.

Positive Moloney reactions occurred more commonly in Schick-negative than in Schick-positive reactors, suggesting correlation between toxoid sensitivity and antitoxic immunity.

The serum of 95.5 per cent of 44 Schick-positive subjects contained less than 0.033 unit of antitoxin per cubic centimeter, and the serum of 77.3 per cent contained less than 0.016 unit per cubic centimeter.

All Moloney-positive persons were readily immunized by three intracutaneous injections of 0.1 cc. of undiluted toxoid or 1:10 diluted toxoid.

Seven of 19 Moloney-negative persons were not successfully immunized by three intracutaneous injections of toxoid.

Six minor reactions to toxoid occurred in 115 intracutaneous injections.

Table 4. *Inverse Relation of Schick and Moloney Reactions.*

Status of Subject	No. of Subjects	Schick-Positive Subjects	Schick-Negative Subjects
		%	%
S + M +	15	35.7	....
S + M −	27	64.3	....
S − M −	41	....	35.3
S − M +	75	....	64.7

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SERIOUS RECURRENT INJURIES OF ATHLETES*

Contraindications to Further Competitive Participation

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CIVILIZATION is undergoing rapid changes. This is an age of ever-increasing speed and change in the multiple aspects of human existence — whether it is speed of a vehicle, on the ground or in the air, or the speed of an electronic calculator. By comparison, organized college athletics change slowly, although, in the past twenty-five years the colleges have become more conscious of their responsibilities for student health.

Among the problems of health in the student population is a large group of diagnoses concerned with trauma. In the experience at Harvard University[1] these represent over 20 per cent of the total diagnoses year after year. This percentage is inclusive of trauma, whether produced by explosion in the laboratory, by a speeding automobile or in a friendly "roughhouse." It is generally agreed that the incidence of accidental deaths is too high, but such accidents continue, regardless of rules and regulations and often because of inadequate enforcement of legal safeguards. Quite apart from the over-all trauma found in the routine of daily living is the trauma produced in the organized athletic program.

After twenty years of responsibility for the surgery of trauma in organized athletics, a review of experience in the treatment and prevention of recurrent injuries is certainly indicated. Furthermore, on reflection, one might even question the criteria established to distinguish the injuries that should not be permitted to recur because of the possibility or probability of a permanent disability to mind, body or limb.

In a well organized college athletic program, where coaching and medical supervision work hand in hand, there is little likelihood that the athlete will leave college with some disabling permanent scar, trick knee or leg paralysis, as a result of sport primarily played for fun. On the other hand, there are graduates who have lost the spleen or one kidney or one eye because of body-contact sports. Still of interest are the multiple instances of fractures in-

TABLE 1. *Types of Injuries, 1932–52.*

INJURY	1932–37	1937–42	1942–47	1947–52*	TOTALS
Sprain	636	426	210	340	1,612
Strain	363	287	96	139	885
Joint contusion	219	73	87	51	430
Muscle contusion	526	350	111	59	1,046
Simple contusion	281	93	103	93	570
Fracture and dislocation	223	232	105	178	738
Laceration and abrasion	264	89	25	37	415
Inflammation and infection	300	131	66	49	546
Internal injury	102	81	39	114	336
Miscellaneous	243	152	67	50	512
Totals	3,157	1,914	907†	1,110	7,090

*To April 15.

†From fall of 1943 until spring of 1946, the University was on a war basis, with organized sports continued only informally and on a limited scale.

*Presented at the Annual Meeting of the American College Health Association, Boston, May 1, 1952.

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volving the teeth in participants in college sports. In the analysis of reported experience 7090 cases of athletic injuries in organized competitive athletics, all fractures and dislocations, as well as an injury to any viscus, are considered serious. In a period of twenty years, the serious injuries represented 15 per cent of the total (Table 1). All injuries recorded were serious enough to require the athlete to refrain from one or more practice sessions or games. Viscus injuries are classified as internal injuries in this table, a group largely represented by cerebral concussion of varying degrees.

An incidence of 15 per cent signifies approximately 1 injury out of each 7. However, to dismiss the matter at that point does not accurately portray it in a true light. The college medical staff is appointed to minimize the untoward results of all the injuries of athletics and to define as graphically and clearly as possible the end-results of treatment in those requiring special care. To dismiss a sprain of a ligament as a minor injury is a grave error: knowledge of the degree of tear and the amount of fibrous scar produced in the healing process and the joint dysfunction resulting therefrom is required for final evaluation.

Certain injuries to ligaments result in avulsion or complete rupture and require prompt surgical repair, as do injuries to tendon or muscle, which occasionally result from athletic trauma. Although sprains and strains rarely cause such extreme damage to tissue, this effect is periodically observed. Widening of the mortise of the ankle joint and internal derangements of the knee are more common than used to be considered possible. All such injuries today are viewed as cause for surgical intervention to correct the resulting joint dysfunction. Over the past five years the complications of sprains and strains presented in Table 2 have been observed.

Complications in sprains are rare. Nevertheless, surgeons treating such injuries should take every precaution to ensure that dysfunction does not result. As officers assigned the responsibility of caring for the health of the students, they should seek to prevent or minimize the degree of permanent dysfunction an athlete suffers. The continued recurrent sprain of any joint leads to the complications listed in Table 2; the prevention of recurrence is therefore desirable. Protective strapping in body-contact sports of every joint with a history of sprain even prior to entry into college has paid dividends in minimizing the resulting dysfunction. Simple joint sprains, if permitted to recur, can cause serious derangements.

The 15 per cent of the total number of athletic injuries involving fractures, dislocations and internal injuries are the concern of all college health departments. Fortunately, with this age group and with increased technical skills available at most colleges, long-bone fractures heal well and in good alignment. However, fractures into joint surfaces or through growing epiphyses may result in disabilities. Elbow dislocations promptly reduced, but inadequately treated in convalescence, cause myositis ossificans and serious joint dysfunction. Shoulder dislocations permitted to recur more than three or four times inevitably require surgical intervention, and a dislocated shoulder, previously operated on, if permitted to recur in athletic trauma will result in a disaster. An athlete who has had a fracture dislocation requiring surgical intervention should never be permitted to return to body-contact sport but may take up some other type of sport. A recent case in my experience is that of a student who sustained a fracture dislocation of the ankle fifteen months ago and is rowing successfully on the varsity squad this season. The return of a patient with a fracture or dislocation to a sport must always depend on his recovery, which can be measured by his ability to perform with normal function all required technics — the normal side and the injured side being judiciously compared in functional testing.

TABLE 2. *Complications of Sprains, 1947-1952.**

INJURY	NO. OF CASES	AVULSED LIGAMENT	DERANGED CARTILAGE	OPERATION REQUIRED	MORTISE WIDENED
Sprained ankle..	162	1	—	1	1
Sprained knee ..	140	1	15	16	—

*To April 15, 1952.

In this group of serious injuries there were 4 luxations of the cervical spine involving spinal-cord symptoms. Two of these cases occurred in college students — 1 in intramural football and 1 in freshman hockey; both resulted in complete recovery. Two other patients, now in college, sustained football injuries in preparatory schools prior to admission to college, resulting in symptomatic recovery. The parents insisted that their sons play football in their freshman year. Such a question posed to college health authorities may be somewhat unusual. With parents' written consent and with the approval of the neurosurgeon who cared for the patient at the time of injury, it is difficult to persuade oneself to deny participation in football. In each case, however, a change in sport activity was easily made, to the satisfaction of all concerned. Such patients should never be permitted to return to body-contact sports.

In cases of viscus injury, patients who have had to have a kidney or spleen removed should not compete in body-contact sport. Those with large laparotomy or nephrectomy scars should not be permitted to expose themselves to the trauma of contact sports. Patients with cerebral concussion that has recurred more than three times or with more than momentary loss of consciousness at any

one time should not be exposed to further body-contact trauma. The college health authorities are conscious of the pathology of the "punch-drunk" boxer. Just how much one should permit recurrence of cerebral concussion in college athletes is a matter of opinion. In all serious cases one should insist upon complete examination, including lumbar puncture in consultation with a qualified neurologist or neurosurgeon. It is my practice to rule out the diagnosis of laceration of the brain in early cases rather than permit the possibility of such an injury to pass unnoticed. One must rule out skull fracture promptly. In twenty years the diagnosis of fracture of the skull has been made in 3 and that of cerebral concussion in 309 cases of head injury; 1 ruptured kidney resulted in prompt and successful surgical intervention, and 2 cases of ruptured spleen have been recognized and the patients operated on successfully.

It seems appropriate to diverge from my specific subject in a meeting of this association and to discuss briefly the mortality in competitive sports. Gonzales[2] has presented a factual report on this subject from the medical examiner's point of view, taking his material from the records of New York City. He has reported two significant facts. Ninety per cent of the 103 deaths recorded in thirty-two years were in four sports, as follows: baseball (43), football (22), boxing (21) and basketball (7). Sepsis was responsible for 25 per cent, and head injuries, including skull fracture or hemorrhage, or both, accounted for 50 per cent of the total. Gonzales did not state how many deaths occurred in organized college, professional and sand-lot competition. Eastwood,[3] on the other hand, reports each year the annual mortality from football. Of interest is his report of the 1945 football season, listing 6 deaths, 3 in high-school and 3 in sand-lot competition. Two members of the American Olympic ski team were killed while in practice in Switzerland in the winter of 1951–52. This association's main purpose is the preservation of health in the college population. Great advances have been made in lessening the morbidity and the mortality, and perhaps a satisfactory level has been reached. It is difficult to explain how so many men and women in colleges today are either maimed or killed in highway accidents, and how students become the victims of suicide and homicide. Properly supervised college athletics, whether intramural or intercollegiate, might reduce the incidence of permanent, crippling injuries in the college population.

So far as the contraindications for further participation in competitive college athletics are concerned, it should be pointed out that in my experience there has been no case in which the end result of even the most serious injuries has required the medical staff to forbid competition in all sports. At Harvard four sports — crew, swimming, squash and tennis — are popular among undergraduates, and these are recommended to many of the patients who have previously sustained serious injuries in body-contact sports. Patients with severe, complicated sprains can be maintained in body-contact sports postoperatively with the daily application of protective adhesive strapping, but only if there has been complete functional recovery. Patients with recurrent shoulder dislocations can be maintained in football with a restrictive harness, but body-contact sports should not be recommended if the shoulder has been operated on. Likewise, students with injuries to kidney, spleen or brain that have required surgical correction or prolonged hospitalization should not be permitted to engage in body-contact sports. The demonstration of the proper type of sport participation rather than the denial of all participation is the proper prescription.

Conclusions

Today there are methods of reducing the incidence of recurrent injury in athletics. Students with certain serious injuries that have required operation or with any large laparotomy or nephrectomy scar should not be permitted to participate in body-contact sports, but may compete in other selected sports. Body-contact sports should not be permitted for any student athlete who has suffered removal of the spleen or a kidney, or who has suffered three cerebral concussions of moderate degree, or one concussion resulting in the diagnosis of laceration of the brain, or loss of an eye.

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MEDICAL PROGRESS

ANTIMICROBIAL TREATMENT FOR VIRAL AND RELATED INFECTIONS*

II. Antibiotic Treatment of Acute Respiratory Infections and Influenza

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THE introduction of the broad-spectrum antibiotics and the demonstration that their effectiveness extends beyond the infections due to gram-positive and gram-negative bacteria to encompass those caused by the rickettsias and the viruses of the psittacosis-lymphogranuloma-trachoma group has raised hopes that these or other antibiotics might prove beneficial against a host of other infections known or assumed to be caused by viruses. Among many practitioners, however, the impression actually prevails, and has been expressed in many medical papers, that these antibiotics are effective against many or all viral infections. Numerous clinical case reports of favorable effects ascribed to these antibiotics in cases of viral or supposedly viral infections have been published. The literature dealing with the antibiotic therapy of primary atypical pneumonia was critically reviewed in a previous Medical Progress report.[1] The present paper presents a similar review of the literature on the use of antimicrobial agents in the prevention and treatment of the common cold, or simple acute undifferentiated respiratory infections,‡ and on their effects in influenza.

COMMON COLD AND UNDIFFERENTIATED SIMPLE ACUTE RESPIRATORY INFECTIONS

Sulfonamides in Therapy

Sulfonamide drugs and antibiotics have been and probably still are used by many physicians in the treatment of the common cold and also in attempts to prevent either its occurrence or the development of the serious or annoying bacterial complications that may follow. Reliable and controlled studies of the effectiveness of sulfonamides in the treatment of colds after their inception have been reported by only a few observers; the important features of four of these studies will be mentioned briefly.

Bordley and his associates[2] used a 2.5 per cent solution of sulfadiazine in 8 per cent triethanolamine (a preparation advocated by Pickrell, one of his associates, for the treatment of burns) to spray the nose and throat of alternate student nurses who reported with symptoms of a cold; the others served as controls and were given a spray of the solvent in the same manner. The treatments were administered by trained personnel to all patients, and they did not know which solution they were receiving. It was found necessary to give the sprays eight times a day during the first two days and five or six times a day for the next two or three days, and a 5 per cent sulfadiazine ointment was applied to the nasal vestibule twice daily. All patients were permitted to use 0.25 per cent solution of Neo-synephrine as needed, but this was rarely employed because the sprays relieved the congestion in almost all cases. Aspirin and codeine were also given to both groups as needed. The irritating cough was almost entirely prevented by the sulfadiazine spray whereas in the control patients this symptom continued for five to fifteen days. Clouding of the antrum was noted in only 2 of the 16 sulfonamide-treated patients as compared with 7 of 14 controls. Nasopharyngeal cultures showed a decrease in beta-hemolytic streptococci in the treated patients but no change in the numbers of alpha-hemolytic or nonhemolytic streptococci. These workers believed that infection was controlled by the sulfadiazine spray; however, the number of patients treated was small, the treatments had to be given too often, and the results as recorded were not very convincing.

Rusk and van Ravenswaay[4] studied the effect of sulfadiazine in patients admitted to an Army hospital for acute febrile respiratory-tract infections, after excluding those who had tonsillitis and those with x-ray evidence of pulmonary infiltration. More than 300 such patients received full therapeutic doses of sulfadiazine consisting of an initial 3 gm. followed by 1 gm. every four hours until well in convalescence; the average total dose was 25 gm. A similar number of comparable control cases were treated during the same period with capsules containing aspirin, phenacetin and caffeine. Both groups were otherwise treated in the same manner. The average numbers of days of fever and of hospitalization were essentially the same in the two groups, as was also the number of patients in whom pneumonia developed.

A controlled study among children with acute febrile respiratory-tract infections was reported by Siegel[5] from Letchworth Village, an institution for

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‡In this paper no distinction is drawn between the common cold and "undifferentiated acute respiratory disease or ARD" as used by the Commission on Acute Respiratory Diseases[3] since these diagnoses were not clearly distinguished in the reports dealing with prophylaxis or therapy with which this review is concerned.

the feeble-minded. Half the patients were given sulfadiazine as soon as symptoms of a cold developed, and the rest were treated symptomatically. Alternation was carried out at first as the cases occurred, but later half the inmates were allocated for treatment by a prearranged plan to avoid selection of cases when several were first observed with symptoms at the same time. A total of 82 infections were treated, and 80 were observed as controls during a period of twenty weeks. The individual dose of sulfadiazine was 0.5 gm. in those weighing less than 50 pounds and 1.0 gm. in those weighing more than 50 pounds; this dose was repeated four times daily for four days or until the patient was afebrile and asymptomatic for at least twenty-four hours. The average duration of fever after treatment was started was one and one-tenth days in those receiving sulfadiazine and three and one-tenth days in the controls; hospitalization was required for only 4 of the former patients and for 19 of the latter. The illness was therefore judged to be appreciably milder and of shorter duration in those receiving sulfadiazine. Some of the infections, however, appeared to be unaffected by therapy; 2 of the patients were found to have lobar pneumonia on the third day of sulfadiazine treatment, and 1 of them died. In other patients, symptoms reappeared after the sulfadiazine was stopped; this was considered to be due either to inadequate therapy or to reinfections.

Cecil, Plummer and Smillie[6] carried out a study in volunteers among hospital personnel through an organized "cold clinic." At first all patients were treated with sulfadiazine, 1 gm. three times a day for four days; subsequently, alternate patients were treated with a placebo of similar appearance. Therapy was started in most cases on the second or third day of symptoms. A total of 48 colds were treated with sulfadiazine, and 24 with the placebo. Successive nasopharyngeal cultures showed a pronounced reduction in the total number of organisms and particularly in the number of pathogens, by the second to the fourth day of sulfadiazine therapy, but these returned to above the starting level within two or three days after this treatment was stopped. The duration of symptoms and the clinical course showed no striking difference from that of the controls although there appeared to be some amelioration of symptoms owing to control of secondary bacterial infections in some cases. On the basis of these results the authors expressed opposition to the routine use of sulfonamides in the treatment of the common cold but favored their use in selected cases as a protection against severe secondary infections.

From the results of these four controlled studies, which involved 463 cases treated with sulfadiazine and 432 comparable cases in which either a placebo or only symptomatic treatment was used, the following conclusions may be drawn: the simple acute febrile respiratory-tract infection or common cold is not favorably affected by sulfadiazine; some of the cases in which there is active or potentially active bacterial infection may be favorably influenced; and not all the complicating bacterial infections are prevented by the sulfadiazine therapy. To avoid the administration of such a drug to patients with colds who would not benefit from its use, it would be necessary to choose for therapy only those with active or potentially active bacterial infections. Since this is difficult to determine at the onset of symptoms of a cold, it seems best to reserve such treatment for those having a previous history of prolonged symptoms following colds and associated with tonsillitis, sinusitis or pneumonia and also for those in whom nasopharyngeal cultures yield a florid growth of potential pathogens that may be expected to be sensitive to the sulfonamides. Such patients should be treated intensively — that is, with full therapeutic doses — until all evidence of active infection has cleared.

Sulfonamides for Prophylaxis

In addition to these therapeutic studies there are a number of reports of the use of sulfonamide drugs in attempts to prevent or reduce the incidence of acute respiratory infections in general or of infections with the hemolytic streptococcus and of rheumatic fever in particular. The latter include the well known mass chemoprophylaxis experiments conducted in the United States Navy and Air Force during World War II; several of the reports of these studies also contain data on nonstreptococcal respiratory diseases.

Before these American studies were reported, Garson[7] had made the claim that sulfanilamide given in lozenge form would bring about a significant reduction in incidence of upper-respiratory-tract infections. This claim was later refuted by Hayden and Bigger,[8] who conducted a controlled study in a British Army training center. These authors gave lozenges, each containing 0.065 gm. of sulfanilamide, to one group of recruits and similar lozenges without sulfanilamide to another. Each recruit kept the lozenge in his mouth until it was completely dissolved and then swallowed it; this was repeated five times daily for sixteen days. High concentrations were thus obtained in the saliva, but blood levels were negligible. The incidence of acute respiratory-tract infections, of which there were more than 1000 cases in each group, was not significantly different in the two groups. These observers concluded that the protection, if any, offered by the sulfanilamide lozenges was so slight as to make this type of prophylaxis not worth the trouble, expense and slight risk involved.

In the initial studies carried out in the United States Air Forces,[9] a reduction of 50 to 75 per cent in the incidence of acute respiratory diseases was attained by mass sulfadiazine prophylaxis. In one of these studies, a dose of 4 gm. given over a period

of forty-eight hours produced a brief reduction in hospital admissions for respiratory illnesses. When 6 gm. was given in three days to other units, there was a 75 per cent reduction in admissions for respiratory disease over a period of twelve days. A similar effect was obtained with a dose of 1 gm. daily, and a comparable reduction in dispensary visits for respiratory infections was obtained in still another group with a dose of 0.5 gm. daily. The most dramatic effect, however, was on the incidence of streptococcal infections.

From another Air Force Technical School, Hodges[10] reported almost complete elimination of streptococcal sore throats and scarlet fever with a daily dose of 1 gm. of sulfadiazine. In this study there was also a marked, though less striking, drop in incidence of lobar pneumonia and other acute respiratory diseases. The relation of the latter to the streptococcus could not always be determined since positive cultures for hemolytic streptococci were obtained in a large number of these cases.

The chemoprophylactic studies carried out in a number of Navy installations all yielded more or less similar and favorable results.[11, 12] The administration of sulfadiazine was begun during a period when streptococcal and other acute respiratory diseases were unusually prevalent; doses of 1.0 gm. and in some cases 0.5 gm. daily were given over a period of several weeks. Altogether, throughout the program, more than 600,000 Navy trainees received daily prophylactic doses of sulfadiazine. In several cases comparable and contemporary groups in which chemoprophylaxis was not employed were available for comparison in the same installations. Such comparisons indicated that this type of prophylaxis had the following effects: the total number of dispensary calls for all respiratory infections was markedly reduced; the total number of hospital admissions for acute respiratory infections was sharply reduced; admissions for streptococcal pharyngitis were reduced 80 to 90 per cent; the incidence of other bacterial infections was also significantly reduced, and those for meningococcal infections completely eliminated; admissions for what had been termed in the Navy "acute catarrhal fever" were variably but significantly reduced; and the incidence of other viral infections — measles, German measles, infectious hepatitis and mumps being mentioned specifically — was not affected. In several installations where catarrhal fever was distinguished from the bacterial respiratory infections and hence most closely approximated the diagnoses of common cold or undifferentiated acute respiratory disease, the reductions in incidence were definitely less marked than those for the bacterial respiratory infections. This differentiation, however, was often difficult to make during the period of great prevalence of streptococcal infections. At Great Lakes, for example, 45.8 per cent of patients with catarrhal fever not receiving sulfadiazine had positive nasopharyngeal cultures for hemolytic streptococci, whereas only 2.4 per cent were positive among those with the same diagnosis who were receiving sulfadiazine prophylaxis. At this station the reduction in incidence of catarrhal fever that followed the introduction of sulfadiazine prophylaxis was similar to that observed with streptococcal respiratory infections.[11]

From all these studies, the exact reduction in incidence of acute nonstreptococcal or viral infections of the respiratory tract was therefore hard to assess, but the over-all reduction in cases diagnosed as catarrhal fever was to about half, and in at least one station it was cut to a fifth as compared with controls not on prophylaxis.[11] The loss of effectiveness in this chemoprophylaxis against streptococcal infections was soon recognized in the Navy and Air Force Hospitals with the increasing spread of sulfonamide-resistant strains of hemolytic streptococci.[13, 14]

In one Army study,[15] mass sulfadiazine prophylaxis, with 1 gm. administered daily to about 20,000 soldiers, was instituted for a period of five weeks; this was started after hospital admissions for common respiratory diseases had reached an alarmingly high rate, about a fourth of the cases being clinically ascribable to hemolytic streptococci. The number of such hospital admissions dropped by a third during the first week and continued to decline for four weeks; a low incidence was then sustained until two weeks after the sulfadiazine administration had been discontinued, when it again rose sharply. How much the incidence of nonbacterial upper respiratory infections was reduced could not be distinguished, but in this study the number of cases of "atypical pneumonia" declined appreciably during the period of prophylaxis, perhaps only by coincidence.

Sulfadiazine was the only sulfonamide used in the various prophylactic studies in the American military units referred to above. At one Air Force Base,[16] a comparative study was made of the prophylactic value of sulfadiazine and sulfapyrazine. A sharp drop in admission rates for all respiratory diseases followed promptly in all the squadrons in which either of these two sulfonamides was given; untreated squadrons showed no appreciable change in the rates of respiratory disease during the same period. Not only did the rates of streptococcal and gonococcal infection drop during the prophylactic period but also there was a coincident and significant decrease in nonstreptococcal respiratory infections, and for these infections sulfadiazine appeared to be somewhat more effective than sulfapyrazine.

A carefully controlled study was carried out at Letchworth Village,[17] the institution for feebleminded children previously mentioned. Thirty children received sulfadiazine continuously for four months, first 1 gm. and later 2 gm. daily; 30 others, who were exactly comparable in the total number of

colds recorded during the preceding year, were observed as controls. In the course of this study there was no significant difference in the frequency or severity of upper respiratory infections in the treated and control children. This is particularly significant since careful and continuous bacteriologic studies were carried out in both groups and complicating bacterial infections were not encountered in either group. The number of colds per child in each group was essentially the same during the period of this study as in the corresponding period of the previous year. Some important changes in the bacterial flora of the nasopharynx with the appearance and spread of drug-resistant strains were noted, but these are not considered here.

From the results obtained in military installations one is therefore led to deduce that the incidence of the common cold, or undifferentiated acute respiratory infection, is significantly reduced by continuous prophylactic administration of sulfadiazine in a daily dose of 1.0 gm. or perhaps even 0.5 gm. However, the following factors make it unwise to place much reliance on these favorable reports so far as the reduction in incidence of simple acute undifferentiated (nonbacterial) respiratory disease is concerned: the high incidence of infections with the hemolytic streptococcus in installations where mass chemoprophylaxis was applied most successfully; the difficulties frequently encountered in evaluating the role of the streptococcus that was so frequently found in cases of simple acute respiratory disease (or "catarrhal fever" in the Navy); the striking effect of the chemoprophylaxis in reducing the incidence of respiratory infections proved to be due to the hemolytic streptococcus as compared with the less striking effect on nonstreptococcal infections; and the fact that the data, as presented, did not permit an adequate estimation of the true incidence of uncomplicated common colds either in the treated or in the control group. On the other hand, the careful and thoroughly controlled study of Siegel and Julianelle,[17] although it was carried out in small groups of children, takes on more significance because bacterial infections were not a complicating factor. In that investigation no reduction in incidence of colds was observed throughout a continuous period of prophylaxis with comparatively larger doses than were used in the military installations. The study of Hayden and Bigger[8] with sulfanilamide lozenges also indicates that the prolonged presence of this agent in high concentrations in the saliva does not prevent the occurrence of common colds.

Penicillin in Therapy

After penicillin became generally available and plentiful, many if not most physicians chose to use this relatively nontoxic and highly effective antibacterial agent instead of sulfonamides for the treatment of almost all acute respiratory diseases since the most frequent bacterial causes of pneumonia or other complications of simple respiratory infections — namely, pneumococci, hemolytic streptococci and staphylococci — proved to be highly susceptible to penicillin. Although one may say without hesitation that this antibiotic has been widely used in the treatment of the acute nonbacterial respiratory infections, there are few reports of controlled attempts to evaluate its effect on the common cold.

One such study was reported by Feinfield and Collen,[18] who treated alternate ambulatory patients as they appeared with symptoms of a cold, either with tablets containing 100,000 units of penicillin by mouth or with placebo tablets of similar appearance; these were given before each meal and at bedtime for four days. At the onset of the treatment both groups were entirely comparable. The patients who completed the treatment were then interviewed and examined. There were 30 who received penicillin; they showed no significant difference in their clinical course from that of the 24 patients who took the placebo.

Another series of cases of common cold in which the patients were treated with a nasal spray consisting of 800 units of penicillin per cubic centimeter and a vasoconstrictor (Paredrine Hydrobromide) was reported by Furlong.[19] A total of 490 colds diagnosed as either infectious or allergenic or a combination of both were treated in children at a school for the deaf. The nasal sprays were administered twice daily, an average of over fourteen treatments per child being given, and there were no unfavorable reactions. The colds cleared within a week in 58 per cent of the children, and 88 per cent were discharged within two weeks. The author considered the results of this treatment more satisfactory than those from any therapy that he had used in this institution during the previous thirteen years. There were no special diagnostic studies and no parallel controls so that these results are difficult to evaluate.

In another study designed to prevent the spread of virulent staphylococcal infections in a maternity ward during epidemics of acute respiratory disease, Knott and Blaikley[20] sprayed the nose and throat repeatedly with a solution containing 1000 units of calcium penicillin per cubic centimeter; this was continued until negative nasopharyngeal cultures were obtained. Streptococci were cleared more rapidly by this method than with sulfanilamide; the incidence of staphylococci was reduced 50 per cent, carriers of this organism being cleared more rapidly than under similar conditions during the previous two years when the spray was not used. The effects on the acute respiratory infection were not reported.

On the whole, it may be stated that there is little information from which one may draw conclusions about the effect of penicillin on the common cold;

what there is suggests that, like sulfadiazine, penicillin cannot be expected to affect the course of the common cold. It may, however, reduce the number of bacterial pathogens in the nasopharynx and prevent or hasten the resolution of infections due to such bacteria. Recent experience with the increasing prevalence of penicillin-resistant staphylococci[21-24] in hospital wards suggests that the results obtained by Knott and Blaikley[20] could not now be duplicated in many hospitals, at least so far as the clearing of staphylococci is concerned.

Penicillin in Prophylaxis

Mention should be made of two reports of attempts to prevent acute respiratory infections by the continuous oral administration of penicillin. Lapin[25] gave 50,000 units to 148 children twice daily for twelve months, and during the same period he observed 110 similar children who did not receive penicillin. These two groups of children had previously been studied and found to have comparable numbers of respiratory infections and days of fever during the preceding twelve months. Those receiving penicillin showed a significant reduction both in the number of respiratory infections (to a half) and in the total number of days of fever (to a fourth) when compared to their own experience in the previous twelve months. In the control children there was no significant difference in the two years.

A study of the effects of mass penicillin prophylaxis on the incidence of colds and on the duration of disability from this cause among a group of volunteers consisting of adults and children over seven years old was reported by Kuh and Collen.[26] This study comprised observations of 4582 patient-months during prophylaxis with penicillin tablets (50,000 units twice daily) as compared with 4682 patient-months in contemporary controls receiving tablets containing calcium carbonate; the average period of observation was more than three months per patient, but some were observed for as long as eleven months. In this study the patients taking penicillin and those taking calcium carbonate showed no significant difference in the number of respiratory or nonrespiratory illnesses, in the number of days lost from work, in the number of days of hospitalization or in the number of patients seeking medical consultations. Nor was any effect discernible on the respiratory infections in other members of the families of persons receiving penicillin prophylaxis. Mild reactions were noted from both the penicillin and from the placebo, and comparable subjective improvement was reported in both groups. There was no evidence that the subsequent use of penicillin was hampered by the penicillin prophylaxis. In this study, no distinction was made between bacterial and viral infections.

These results appear to be contradictory. The more extensive study of Kuh and Collen,[26] which was carried out chiefly in adults, indicates that the incidence of acute respiratory infections cannot be influenced by mass penicillin prophylaxis as carried out by them. The nature of the illnesses encountered by these authors or by Lapin[25] is not clear, but since fever was a prominent feature in the infections observed by the latter, it seems likely that bacterial infections played a prominent role in many of the respiratory illnesses that he observed. The possibility of favorably influencing such bacterial infections is indicated from the uniformly good results obtained in the studies on the prophylaxis of streptococcal infections and of recurrences of rheumatic fever by penicillin.[27-30] Although there may be important changes in the bacterial flora of the nasopharynx during continuous penicillin prophylaxis,[31, 32] the appearance of penicillin-resistant Group A hemolytic streptococci has not been observed[28]; this is in contrast to the recent experience with staphylococci.[30] The incidence of the uncomplicated common cold, however, is probably not influenced by penicillin prophylaxis.

Aureomycin and Chloramphenicol

Since the broad-spectrum antibiotics are highly active against a much greater variety of respiratory pathogens than penicillin, including gram-positive and gram-negative bacteria, the rickettsia of Q fever and the psittacosis virus, these antibiotics have naturally been considered to be more suitable than penicillin and sulfonamides for the treatment of common respiratory infections. They have therefore been used both early in the course of these diseases, when differentiation and accurate diagnosis is difficult, or later because the greatest variety of specific infections or their bacterial complications might be affected. Here, again, in spite of the widespread use of these agents, the number of adequately documented studies of their effects on the course of the common cold or their efficacy in preventing acute respiratory infections is small indeed.

At the 1949 meeting of the Association of American Physicians, Kneeland[33] reported a study in which full therapeutic doses of aureomycin, 4 gm. per day, were given for forty-eight hours to 20 patients with typical common colds. The first 10 of these were alternated with similar cases treated with a placebo consisting of lactose. Among the latter a dramatic effect was observed in 1 patient, the symptoms of 2 others showed an altered pattern, and 7 obtained no effect; among those treated with aureomycin 6 were considered dramatically improved, in 6 others the disease pattern appeared to be altered, and 8 showed no effect. Interestingly enough, 2 of the patients receiving the placebo of lactose had loose bowels, and 2 showed other untoward symptoms, thus emphasizing the importance of controlling all aspects of such studies. Kneeland

and his colleagues believed that for this experiment to have positive significance all or nearly all the colds should have been promptly aborted; since nearly half the cases showed no effect, they concluded that aureomycin was ineffective against the agent or agents causing most minor upper respiratory disease in man.

In a survey study on the effect of aureomycin on acute respiratory diseases, mostly in children, Schrick[34] used this antibiotic in 4 cases of common cold, in 30 cases of nonbacterial exudative tonsillitis, in 4 of "acute respiratory disease" and in 7 patients with "infectious croup" not due to diphtheria or to *Haemophilus influenzae*. She considered the clinical course of the great majority of these infections to have been shortened by the treatment with aureomycin. In particular, 6 of the 7 patients with infectious croup were well within twenty-four to thirty-six hours after aureomycin was started. During the previous winter the continuous use of 100,000 units of penicillin twice daily, given in attempts to prevent colds in susceptible children, failed to prevent the occurrence of cases of croup in such children during an outbreak, nor did the penicillin influence the course in those who contracted the disease.

In a similar study in adults,[35] febrile patients with clinical influenza or acute respiratory-tract infections in whom virus studies failed to reveal an influenzal etiology all became afebrile and asymptomatic within twelve to twenty-four hours after the first dose of oral aureomycin. There were no controls in this study, and the role of the aureomycin in the rapid recovery of these patients could not be properly evaluated. The same statement is true of the cases reported by Cohen and Schwartz,[36] who used chloramphenicol in the treatment of 8 patients with uncomplicated acute respiratory diseases and 7 patients with laryngotracheobronchitis with negative lung findings on x-ray examination who had previously failed to respond to treatment with penicillin. The patients were of all ages and were seen in private practice. These authors gained the impression that chloramphenicol had a favorable effect in these patients, some responding quickly and others more slowly.

Finally, Hoagland and his co-workers[37] reported a carefully controlled study from a military installation in which aureomycin and inert yellow capsules were dispensed to alternate patients when they first reported with local or constitutional symptoms of a cold. The patients were then seen by the authors during the next seventy-two hours, and an estimate was made of the effects of the treatment on the course of the symptoms. Of the 155 patients who received aureomycin, 67 took 1 gm. daily, and the other 85 received 2 gm. each day; the proportions of all these patients who were considered cured in twenty-four hours, moderately improved, slightly improved or showing no beneficial effect was strikingly similar to the percentage in whom the corresponding effects were noted from the placebo. About half the patients were reported as being rapidly cured or showing moderate improvement after taking the inert substance.

From these studies it should be clear that the evaluation of therapeutic effects in such a variable and often mild disease as the common cold is extremely difficult in the absence of careful studies with comparable controls selected at random. Although the observations in the general surveys of the effectiveness of aureomycin and chloramphenicol in simple acute respiratory infections suggested that these antibiotics had a beneficial effect, the results in the controlled studies of Kneeland and Hoagland and their respective co-workers leave little doubt that the uncomplicated common cold is not favorably affected by aureomycin, and the same reservation undoubtedly holds for the other broad-spectrum antibiotics, terramycin and chloramphenicol.

Patulin and the Common Cold

In 1943, Raistrick and a group of British collaborators[38] reported the isolation and chemical properties of a new antibiotic, patulin, which was a metabolic product of *Penicillium patulum* and had considerable bacteriostatic activity against gram-positive and gram-negative organisms. Some of this antibiotic was sent for special studies to Dr. W. E. Gye,[39] director of a large cancer-research laboratory. At the time when this material reached him, Dr. Gye was in the second stage of a severe common cold. In a spirit of inquiry, he prepared a solution of this patulin, which he used as a nasal douche, and was much impressed with the striking relief that he experienced. He then persuaded some of his medical colleagues and other friends to try it on their colds, and they, in turn believed that they too obtained unusually rapid relief and were spared some of the long and unpleasant aftermaths of their colds. The febrile course of influenza in 1 patient was not affected. Of the professional observers whom Dr. Gye considered reliable, only 1 reported no improvement. The reports from nonmedical friends were not considered reliable; some had difficulties with the nasal douchings, and others exaggerated the benefits. The earliest symptoms of coryza were not completely stopped, but the findings seemed of sufficient interest to warrant a more extensive clinical trial.

Such a trial was undertaken by Hopkins[40] in a Navy establishment during a four-month period when common colds were prevalent. Solutions of patulin were used as a nasal spray or were snuffed up from the hand every four hours during the day. The results were considered encouraging; 57 per cent of 95 patients treated with this solution recovered completely within forty-eight hours as com-

pared with only 9.4 per cent of 85 subjects who received similar treatments with the control of buffer solution without patulin. Favorable reports were also obtained from selected observers suffering from colds, who kept careful notes of their symptoms. Some of the local complications, such as sinusitis, were not relieved, presumably because they were not reached by the solution. Statistical analysis of these results showed them to be highly significant.[41]

No sooner had the results been published than Stuart-Harris and his co-workers[42] communicated the results of a similar study, later reported in detail,[43] which failed to confirm the beneficial effects observed by Gye[39] and Hopkins.[40] They used nasal instillations of drops of a buffered patulin solution in 50 soldiers with ordinary afebrile coryza, a similar number of controls selected at random being treated with the buffer solution without patulin. Each patient received eight treatments in forty-eight hours. The duration of symptoms both before and after treatment was started was the same in the two groups. In the subjective evaluation of the patients an equal number in each group believed that the treatment had a good effect, and the same number in each group considered that the treatment they received had no effect.

Because the discovery of an effective treatment for the common cold was considered to be of great practical importance and in view of the contradictory results obtained in these two series, one from the Navy and the other from the Army, the Medical Research Council undertook an extensive reinvestigation of the claims.[44] Trials were carried out among the personnel of eleven factories and three post-office units and the pupils of two public schools. Great care was taken to choose cases at random for treatment with patulin and with a control buffer solution, neither patients nor investigators knowing which solution was being dispensed until the end of the study. A total of 668 patients were treated with eight to twelve nasal instillations each of the patulin solutions, and 680 were similarly treated with the buffer control. Only 13 per cent of each group was cured in forty-eight hours; an additional 60 per cent of the patulin-treated patients and 64 per cent of the controls were improved during that time.

The explanation for the divergent results in the Navy as compared with those obtained in the Army or among various groups of civilians is not clear. It could only be concluded that patulin did not affect the clinical course in most cases of the common cold. These trials again emphasized the difficulties in assessing the effects of therapeutic agents in the common cold, particularly in view of the frequent lack of objective signs that can serve to check the patient's response.

Comments and Conclusions

It is apparent that some favorable effects on acute respiratory disease have been reported from each of the sulfonamides and antibiotics that have been used; it is equally clear, however, that none of these favorable results could be confirmed under carefully controlled conditions by other observers using the same agents. An important feature, however, has been the uniformity with which acute bacterial infections have been influenced by all these agents; the most favorable effects on acute respiratory infections in general, or even in cases that have been considered to be acute nonbacterial respiratory infections, have been in groups, or under conditions in which infections with susceptible bacteria, particularly hemolytic streptococci, have been prevalent during the period of the studies.

It seems reasonable to conclude, therefore, that none of the antimicrobial agents have been unequivocally demonstrated to have a favorable effect in the treatment or prevention of the uncomplicated common cold or the simple, acute nonbacterial respiratory disease. The routine use of these agents for the treatment or prevention of common colds does not therefore seem warranted. On the other hand, they may prove highly useful in cases in which bacterial complications are present or may be anticipated or during periods of high prevalence of infections with hemolytic streptococci or other susceptible bacteria.

Infections Due to Influenza Virus

Chemotherapeutic Agents

The chemotherapeutic studies on the common cold have been seriously hampered by the fact that the etiologic agent cannot be readily isolated, propagated and transmitted to susceptible lower animals so that carefully planned experiments cannot be executed in the laboratory. The same limitation prevailed with epidemic influenza until 1933, when the viral etiology of this disease, at least in the form in which it was recognized at that time and in all epidemics since then, was firmly established. The susceptibility of mice, and particularly of chick embryos, to the influenza viruses and the ease of handling the infections of these hosts in the laboratory have made possible large-scale survey studies of various chemicals, for their potential activity against infections with the influenza virus. These studies have certain distinct advantages over direct observations of spontaneous infections in human beings, particularly because the factor of complicating infections with bacterial pathogens can be controlled more readily in the experimental host.

One of the most extensive surveys of chemicals for their effectiveness against intranasal infection of mice with influenza A virus was reported in 1943 by Andrewes, King and van den Ende.[45] They tested

115 substances, which included varying numbers of the following types: long-chain compounds containing guanyl groups; alkaloids, including quinine and optochin; arsenicals; antimonials; sulfonamides; gold compounds; essential oils; salicylates; surface-acting agents; peroxides; formaldehyde compounds; nitro compounds; dyes; agents that fix copper; and miscellaneous compounds, including penicillin. The dyes included representatives of divergent types such as acridines, pyronines, oxazines, thiazines, selenazines, phenazines, diphenylmethanes and triphenylmethanes and azo-dyes. Not one of these 115 compounds, in nontoxic doses, had any beneficial effect on the infection.

Several additional studies carried out prior to 1944 were summarized in tabular form by Kramer, Geer and Szobel[46]; they involved chiefly tests in mice with sulfonamide and sulfone derivatives, quinine and quinoline compounds (most of these in combinations with sulfonamides and sulfones), some flavines, certain miscellaneous chemicals and antiseptics and a few additional antibiotics — namely, tyrothricin, tyrocidin, gramicidin and subtilin. The only positive results were those reported by Climenko, Crossley and Northey,[47, 48] who observed significant protective effects from disulfanilamide and some of its derivatives in mice infected with influenza virus of low virulence. The protective effect of disulfanilamide was confirmed by Long and Bliss,[49] but only when the drug was given parenterally; they, too, failed to protect against virulent infections. These results, however, have not received general confirmation.

In this connection the report by Dochez and Slanetz[50] on the treatment of canine distemper with sodium sulfanilyl sulfanilate is worth recalling, since the etiologic agent of this infection was thought to be similar to the influenza virus. This publication caused considerable interest and excitement because it appeared to represent the first time that a chemical was shown to have definite therapeutic action in an infection with a filtrable virus. Both the preventive and curative effects of this drug were demonstrated in ferrets experimentally infected with the canine-distemper virus either as a dried vaccine or as fresh virus contained in filtrates of spontaneously infected dogs. The authors demonstrated equally dramatic effects in spontaneous distemper in 28 dogs and in 18 cats suffering from a spontaneous disease called cat distemper or influenza. Long and Bliss[49] critically reviewed the results of Dochez and Slanetz and those of others, most of whom failed to confirm their findings with the same or other sulfonamides, except for the recoveries in animals treated for the spontaneous disease. Long and Bliss stressed the importance of secondary bacterial infections in dog distemper and referred to an outbreak of infections that were diagnosed as this disease. However, careful bacteriologic studies revealed the illness to be due to Group C hemolytic streptococci. Dramatic cures were obtained with sulfanilamide in that outbreak.

I had an isolated experience of this sort when called by a surgical associate to see a dog that was almost moribund with what was clinically diagnosed as distemper acquired late in convalescence from an extensive surgical operation. After subcutaneous injections of a solution of sodium sulfanilyl sulfanilate, the dog recovered rapidly; however, a blood culture taken before the first dose revealed more than 100 colonies of a Group C hemolytic streptococcus per cubic centimeter of blood, and subsequent blood cultures were negative. Few studies of natural infections that have been successfully treated have been controlled both for the specific virus and for the possible presence of complicating bacterial infections.

In a number of additional reports one or more groups of chemicals that are known to have significant biologic activity or to have structures related to biologically active chemicals have been tested for activity against infections with one or more strains of influenza virus in mice, chick embryos or both.[51-68] Most of these studies have yielded essentially negative results; a few, however, were of interest because some degree of activity was demonstrated, and the findings may suggest possible leads for further investigations. Certain acridine compounds, because they had shown beneficial effects against rickettsial infections or inhibited the growth of bacteriophage (bacterial viruses), have also been tested against infections due to influenza virus. In preliminary experiments, Green, Rasmussen and Smadel[56] showed that Nitroakridin 3582 inhibited the growth of influenza B virus in embryonated eggs but primarily when a small inoculum was used. Subsequently, Rasmussen and Stokes[63] reaffirmed the retarding effect of this substance and showed some effects from certain related compounds and from a cobaltous salt. The most active of these acridines — namely, Nitroakridin — did not act on the virus in vitro; it had an appreciable toxicity for the chick embryo and had no chemotherapeutic effect on influenza-virus infection in mice. Among compounds found to be inactive the authors included pentamidine and chloramphenicol (Chloromycetin).

Several lactones have been found to have some effect on infection with influenza virus in mice.[67] Proflavine, when injected in concentrations that were not virucidal, a few hours before or after inoculation of chick embryo with influenza B virus, inhibited the multiplication of that virus but had no effect on influenza A virus.[62] In a study on the effect of various dyes,[64] a number were found which affected the influenza virus in vitro; only 2 of them affected the course of the infections in mice, but these did so only when given intravenously in doses that approached the lethal level. They seemed to

be more active against PR8 than against the related WS strain of influenza A. One group of aromatic amidines — pentamidine, heptamidine and hexamidine, but particularly the last — was found to exert some inhibitory effect on the growth of influenza A virus in embryonated eggs; they had no effect on the virus in vitro or against infections in mice.[60] Eaton and his co-workers[65] confirmed these findings and also showed that pentamidine and propamidine inhibited infections with small doses of influenza B virus in chick embryos and retarded the growth of virus in de-embryonated eggs; they too failed to demonstrate any activity with these compounds in mice. However, these compounds exerted some inhibitory effect on the multiplication of the virus in tissue cultures.[66]

A number of essential metabolites, enzymes or vitamins, their analogues or antagonists and other substances active in cell growth or influencing cell metabolism have also been tested against experimental infections with the influenza virus. General anesthetics have proved to be ineffective against such infections in mice.[61] Certain amino acids in concentrations that were not directly toxic were found to retard the growth of influenza virus in tissue cultures.[64] Cytochrome C was without effect in mice.[61] Ascorbic acid, on the other hand, was found by Knight and Stanley[62] to exert a significant protective effect against influenza A infection in mice; this was demonstrated when the virus suspension and ascorbic acid were first mixed in vitro and then inoculated. This action was considered by Klein[63] to be due to the liberation of hydrogen peroxide by the ascorbic acid during the period when they were kept together in vitro. He showed that the same effect could be duplicated if the virus suspension were mixed with the amount of hydrogen peroxide that theoretically was liberated by the action of the ascorbic acid. The reaction between the virus and the ascorbic acid, however, was inhibited by the addition of catalase in vitro. Since catalase is available in animal tissues, vitamin C cannot be expected to have any inhibiting effect on the virus in vivo if it is administered separately from the infecting dose.

In a survey of vitamin-analogues,[68] one compound, 2-5 dimethylbenzimidazole, which is chemically related to a moiety of vitamin B_{12}, was found to restrict the multiplication of the PR8 and Lee strains to about 10 per cent of control values; this action seemed to be mediated through some cellular metabolic mechanism in the host, possibly nucleic acid metabolism, not directly related to respiration. Hoyle[59] had found that certain triphenylamine dyes retarded the growth of influenza A and considered that this might be due to an interference with the metabolism of ribonucleic acid in infected cells. In another survey,[67] 150 compounds were tested in maximum tolerated doses against a standard dose of influenza virus in chick embryos. Two compounds — a polymerized sodium salt of benzoid sulfonic acid and Congo red — appeared to be effective if given several hours after the infecting inoculum. The effect of the former was partially reversed by tryptophan, whereas that of Congo red was reversed by nicotinic acid, calcium pantothenate or thiamine hydrochloride.

From a practical point of view one may summarize these findings briefly by saying that the extensive searches of many competent workers for effective chemotherapeutic agents have not uncovered any that could be used safely in human beings and that offer any promise of curing or exerting a favorable influence on infections with the influenza virus.

Antibiotics

Penicillin and chloramphenicol have already been mentioned among the agents that have failed to influence experimental infections with influenza virus.[45, 63] Streptomycin, likewise, has no effect. Indeed, because neither penicillin nor streptomycin affects influenza viruses, the combination of penicillin and streptomycin, in large doses, has been utilized in many laboratories as a means of eliminating contaminating infections with gram-positive and gram-negative bacteria in chick embryos during attempts to isolate influenza viruses from sputum or infected tissues.[69, 70] In the earliest reports on the activity of aureomycin[71] and of chloramphenicol[72, 73] in experimental viral and rickettsial infections, each of these agents was found to be inactive against infections with influenza viruses.

The clinical study carried out in this hospital on the effect of aureomycin in various respiratory infections[35] included observations on 18 patients who had infections of more than average severity that were proved to be due to influenza A; they occurred during an epidemic and were accompanied by bronchopulmonary involvement in most cases. Pathogenic bacteria of possible significance were isolated from throat or sputum cultures in only a few of these patients. Marked and rapid improvement occurred in direct relation to the administration of aureomycin and was quite impressive in all but 3 of the patients. However, no parallel or comparable cases were observed without aureomycin therapy or under other forms of therapy so that an accurate evaluation of the effect of aureomycin or comparison with other agents is not warranted.

A controlled study on the effect of aureomycin in the treatment of influenza was carried out in an Army hospital during an epidemic of influenza A'. In that study,[74] 150 consecutive unselected cases were observed; 60 of them were treated with aureomycin, 43 with penicillin, and 38 without antibiotics. The course of the illness in these three groups of cases selected at random was indistin-

guishable when judged by the mean total duration of illness, of fever or of hospitalization.

In the original paper on terramycin,[75] it was noted that high concentrations of this agent appear to inhibit infection of the chick embryo with the PR8 strain of influenza A. Vinson and Walsh[76] showed that as much as 5 to 10 mg. of terramycin hydrochloride per egg administered up to three hours before or up to one hour after infection were required to inhibit the development of hemagglutinins in more than half the embryos inoculated with ten infective doses, and 10 mg. of the sodium salt had a similar inhibiting effect in eggs inoculated with 100 infective doses. Tests for infectivity were not carried out with the fluids of the treated embryos in which hemagglutinins did not develop; in a comparable study with aureomycin and the mumps virus, the infectivity of fluids from treated embryos was the same as that of control eggs although hemagglutinins were inhibited.[71] Concentrations of terramycin similar to those attained in the fluids of protected embryos did not inactivate the virus in vitro, nor did they inhibit hemagglutination of the virus. These effects could not be duplicated with influenza B even when smaller infecting doses were used. Moreover, oral, intravenous or intramuscular administration of terramycin did not influence the course of infection in mice induced by the PR8 strain of influenza A.

Kass, Barnes and Finland[77] showed that carefully neutralized terramycin in doses up to 20 mg. per egg had no effect on the infectivity, hemagglutinability or rate of growth of the PR8 virus in the allantoic sac of chick embryos. At a pH of 3.6, which was readily attained in broth with terramycin hydrochloride in the higher doses used in chick embryos, influenza A virus was inactivated within five minutes. Large doses of terramycin given orally or subcutaneously did not alter the time of death or the mortality rate in prophylactic or therapeutic experiments in mice. Five patients with influenza A′ infection, which was proved in each by isolation of the virus, were treated with terramycin orally; 4 became afebrile promptly after administration of the terramycin, and the fifth recovered slowly. The findings could not be interpreted as indicating a beneficial effect from terramycin on the infection. Blake, Friou and Wagner[78] also obtained no effect from terramycin in a case of influenza. In another study, Kass, Lundgren and Finland[79] failed to demonstrate any increase in resistance of mice or rats to the acute toxic action of influenza A virus by the oral or subcutaneous administration of aureomycin or terramycin.

Conclusions

From all these reports it appears that none of the useful antibiotics that are now available can be said to have any significant beneficial effect on infections with influenza virus. At present, the use of these antibiotics in the treatment of epidemic influenza can be considered as justifiable only as a means of preventing or treating serious complicating bacterial infections.

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MEDICAL INTELLIGENCE

QUININE FOR THE RELIEF OF PARESTHESIA OF UNDETERMINED ORIGIN

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THE traditional pharmacologic importance of quinine has been due to its effect on malaria parasites and to its reputation as a stimulant of uterine contractions. More recently, it has been found of value as a muscle relaxant in various types of myotonia. The curare-like action of quinine in this condition has led to its wide use in an analogous clinical entity characterized by night cramps, usually in the calves of the legs. This syndrome, when not the result of frank arterial insufficiency, usually responds promptly to 0.3 gm. (5 gr.) of quinine sulfate given prophylactically at bedtime or to the same dose given therapeutically as soon as cramps are experienced. After a week's routine prophylactic administration, many patients are able to discontinue it for prolonged periods without a recurrence of symptoms.

In the hope of relieving the muscular aching of a tense middle-aged woman with "psychogenic rheumatism," 0.3 gm. of quinine sulfate was prescribed at bedtime. Although this failed to relieve her discomfort, in contrast to its effect in true night cramps, she volunteered the information that she was free of the nocturnal numbness and tingling of the right upper extremity that had troubled her for the past month. Examination had failed to reveal any nerve-trunk tenderness, impairment of tactile or vibration sense, or impairment of motor function of the median, ulnar or radial nerves. Abduction of the arms did not reduce the amplitude of the radial pulses, nor did elevation, designed to stretch the brachial plexus, reproduce the paresthesia complained of at night. A purely psychologic effect seemed unlikely since the patient had obtained no relief from orthodox vitamin therapy specifically prescribed for the complaint and finally abandoned. Furthermore, when the quinine was omitted, the glove-like paresthesia, limited to the right hand, promptly recurred. This again responded to the administration of quinine.

Since I had observed that glove paresthesia, without any other stigmas of conversion hysteria, had been a fairly common complaint, it seemed worth while to give the drug a trial in patients who presented this symptom without objective neurologic findings or demonstrable cause. Patients with combined system disease were excluded after quinine had failed to alleviate the paresthesia of a patient with pernicious anemia that had persisted in spite of doses of vitamin B_{12} more than sufficient to effect hematologic remission. Patients with Raynaud's disease were also excluded since the relief of pain, numbness and tingling incident to vasospasm that had been obtained in 1 case could not be duplicated in a number of others. Patients whose paresthesia was attributable to extreme humeral abduction during sleep, which might cause either impaired arterial circulation or abnormal tension on the brachial plexus, were omitted from this study, as were elderly patients whose manual paresthesia was suspected of being due to anoxemia of the sensory cortex presiding over this part. Two cases raised this suspicion because of the patients' age and their complaint of clumsiness in the involved hand. No weakness, clumsiness or sensory impairment was demonstrable, however, and they experienced immediate relief from 0.3 gm. of quinine sulfate twice a day. In none of the 7 patients in this report was there any true pain, nerve-trunk tenderness, impairment of tactile, pain or vibration sense, or inco-ordination or weakness in the extremity involved. Color and skin temperature were normal, and pressure over the scalenus anterior muscle evoked no pain. A patient who had complained of paresthesia of the entire left upper extremity, day and night, for three weeks, noticed that carrying bundles or putting her arm over her head increased the severity of the symptoms but was not wholly responsible for them. Although quinine sulfate in a dosage of 0.3 gm. twice a day did not give the complete relief experienced by the other patients, it decreased the frequency and severity of the spontaneous attacks of paresthesia and ameliorated the aggravation due to carrying of bundles, which probably stretched the brachial plexus.

This group consisted of 1 man and 6 women ranging in age from thirty-eight to seventy-six years. None of them were suffering from any significant disease during the period of observation although the oldest had mild asymptomatic hypertension and an inevitable degree of arteriosclerosis. The duration of symptoms varied from a few days to seven years. In 4 of the 7 patients the numbness and tingling was noticeable only at night. In all 7 cases one or both hands were involved, but only the male patient complained of paresthesia of the lower extremities as well. All 7 cases responded to quinine within twenty-four hours, usually experiencing relief the night the drug was first taken; 0.3 gm. taken at bedtime was sufficient for those complaining of paresthesia only at night. Those with daytime symptoms received the same dosage

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night and morning. The symptoms were completely relieved in 6 of the 7 cases. In the patient whose symptoms could be aggravated by brachial-plexus traction, quinine materially lessened the frequency and severity of the spontaneous attacks so that she was quite reconciled to such symptoms as remained. Some of the patients who have been followed for over a year have been able to discontinue quinine after days or weeks of therapy without a recurrence of symptoms. Some have had to resume it from time to time because of a return of paresthesia after varying intervals of freedom. In this respect their experience closely resembles that of patients with night cramps. None experienced cinchonism.

In the absence of any demonstrable lesion or cause it is futile to speculate about the mode of action of quinine in this type of paresthesia. If the relief is due simply to the analgesic action, like that of the salicylates, on the central nervous system, it appears to be superior to aspirin in this particular condition. It is realized that glove and stocking paresthesias are frequent symptoms of conversion hysteria. None of these patients, however, had any other stigmas of hysteria, and it seems hardly warranted to make a diagnosis of hysteria on the basis of a single symptom that is common to a variety of disorders. The apparent benefit of quinine is probably not due wholly to suggestion, for no patient was told in advance what the effect would be and leading questions were carefully avoided in later attempts at appraisal. Furthermore, some of the patients with long-standing symptoms had tried without benefit a variety of measures for which high hopes had been held out. No claim of priority is advanced for the therapy employed although a perusal of the current medical literature has not revealed similar reports. This preliminary report is offered simply in the hope that others may be successful in relieving a common and vexatious symptom and perhaps in elucidating the mechanisms involved.

276 Bridge Street

MASSACHUSETTS PHYSICIANS ART ASSOCIATION

9. Beach Grass

Exhibited at Massachusetts Medical Society, 1952

Oil Painting by

BASIL E. BARTON, M.D.

Visiting Physician
Faulkner Hospital

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38411

PRESENTATION OF CASE

A fourteen-year-old girl was admitted to the hospital because of enlargement of the right breast.

About eight months before admission the patient first noted that the right breast was slowly and painlessly becoming larger than the left. The breast continued to enlarge slowly and steadily without any associated symptoms until six weeks before admission, when there was an acceleration in the rate of the enlargement, accompanied by some tenderness in the breast and a small amount of clear, yellow discharge from the nipple.

FIGURE 1.

Menstruation had not been definitely established, but for the six weeks before admission the patient had had periodic episodes of vaginal spotting lasting two or three days and occurring every one or two weeks, without any consistent periodicity. Her general health was good. There was no history of trauma to the breast. Her mother had died of carcinoma of the stomach at an early age.

Physical examination revealed a well developed, well nourished girl in no distress. The right breast was approximately four times the size of the normally developing left breast (Fig. 1). The skin was violaceous and slightly warm to touch. The nipple was flattened, and there were distended veins overlying the surface of the breast. The breast parenchyma felt tense, and the process was diffuse throughout the whole breast except for a fluctuant area just above and medial to the nipple. There was no distinct tenderness, and no definite nodules; no fluid could be expressed from the nipple on gentle pressure. There were no palpable axillary lymph nodes. The left breast was normal, and there were no other abnormal physical findings.

The temperature was 98.3°F., the pulse 80, and the respirations 20. The blood pressure was 130 systolic, 80 diastolic.

A urinalysis was negative.

On the second hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. NATHAN TALBOT*: It seems to me that my task is not so much to try to make a diagnosis on the basis of the evidence given as to consider the validity of the diagnostic biopsy. This comment is made because I have seen a number of children in whom one breast has been irretrievably disfigured as a result of unnecessary and overgenerous biopsy early in life.

Decision concerning biopsy should presumably be based upon a consideration of the differential diagnosis, which in turn depends partly on the age of the child, especially the physiologic or developmental age. In this connection I believe that cancer is almost unheard of in preadolescent children.

Benign and presumably physiologic development of one or both breasts is seen fairly commonly in female infants and children who may otherwise seem to be completely preadolescent. Under this circumstance there is a palpable and at times visible mass of breast tissue beneath the nipple. This may enlarge to such an extent that one or both breasts resemble those seen in true adolescence. Yet such other signs of adolescent development as vaginal cornification, pubic and axillary hair growth and increased urinary estrogen and ketosteroid excretion are absent. The histologic appearance of virginal hypertrophy of the breast is similar to that seen in adult male gynecomastia. The breasts in this condition either may subside spontaneously in a number of months or may remain appreciably developed until adolescence supervenes.

The next condition to consider is ordinary adolescent breast development in girls. It is a well known clinical fact that one breast may bud and grow before the other one shows any changes. This

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is thought to be due to differences in sensitivity on the part of the mammary glands as end-organs. In due course, both breasts attain approximately equal growth.

Very occasionally, girls are born with a congenital lack of breast tissue on one side. Under this circumstance, there is permanent inequality of breast development.

Inequality of breast size also can result from the opposite condition of congenital hyperresponsiveness to normal adolescent endocrine influences. In other words, there may be a congenital tendency to gigantism of the breast on one or both sides. Here, growth of the mammary gland is thought to be unusually responsive to normal amounts of circulatory hormones. This condition is often called simple or virginal hypertrophy of the breast.

To be contrasted with these benign congenital and physiologic breast conditions are certain pathologic states. Among these, tuberculosis with cold abscess formation should be mentioned in the interest of completeness. This must be a very rare disease in children living hereabouts. According to the literature, its existence is usually revealed by the presence of a draining sinus. Such a sinus was not present in our patient.

Next, there are various types of fibroadenoma, which can grow quite large and which can be so diffuse as to appear to be just hypertrophied breast tissue. These fibroadenomas may be encapsulated and benign. On the other hand, they may develop into a condition, cystosarcoma phyllodes, which is at least potentially malignant; this disease is fully described in a recent paper by Treves and Sunderland.[1] Although it usually is seen in women, it has been recognized in a girl of fifteen years. The breast in cystosarcoma phyllodes is likely at first to undergo a rather long period of relatively slow growth and then suddenly to start growing at a more rapid rate, as in the case under discussion. Except for the complaint of increased size, the condition is symptomless. There are no major nipple changes. The veins may be prominent, apparently as a result of partial obstruction to venous outflow by the lesion. Lobulation and fluctuant cystic areas similar to the one described in this case may be recognizable on clinical examination. The disease may have a benign course or may become malignant. The latter fact makes it important to recognize the condition.

One other diagnosis that comes to mind is carcinoma. I find it difficult to believe that this child had a straightforward carcinoma of the breast. The lesion did not start with a lump; there was no nipple change, no fixation of underlying structures and apparently no tendency to ulceration as might be expected in a lesion as advanced as that shown in this case.

In conclusion, this child's condition does not appear to fall securely into one of the genetic or physiologic and hence benign categories, for she showed changes suggestive of cystosarcoma phyllodes, a possible, malignant condition. On this account it appears that the biopsy procedure was clearly indicated and fully justified.

Dr. Joseph C. Aub: I certainly think this child had to be biopsied. I would rather guess that she had a papillary cystadenoma.

A Physician: Did the vaginal spotting have any relation to the condition in the breast, or was it coincidental?

Dr. Talbot: Many normal girls have irregular bleeding or spotting during the first months after the menarche. This usually disappears within two years, by which time most girls are having regular, ovulatory rather than irregular, anovulatory menstrual cycles. Thus, I doubt if the spotting bore any important relation to the rest of this picture.

Dr. Ira T. Nathanson: I saw this patient three months before admission, when the findings suggested asymmetrical virginal hypertrophy. There was something, however, that bothered me a good deal since the process was not entirely consistent with the usual type of hypertrophy. The child was asked to return in a month for further observation, but because of a series of circumstances, she did not return at the appointed time. The change that had occurred in the breast in the interval between visits was unbelievable. The involved breast was thrice the size of the opposite normally developing breast, and the changes were considerably different from those noted on the first examination. As demonstrated in the photograph (Fig. 1), the skin was beginning to break down, presumably from the pressure on the lateral side. It seemed to me that this was not an asymmetrical mammary development; the possibility of malignant neoplasm or of degenerating fibroadenoma, although unusual, had to be entertained. Cystosarcoma phyllodes was strongly considered even though it is extremely rare in females of this age.

Clinical Diagnosis

?Cystosarcoma phyllodes.

Dr. Talbot's Diagnosis

Cystosarcoma phyllodes.

Anatomical Diagnosis

Cystosarcoma phyllodes.

Pathological Discussion

Dr. Nathanson: At operation I elected to make a medial periareolar incision because the skin seemed to be in the best condition in that area and also that was the point of maximum fluctuation. When the incision was made through the fascia, it became clear that there was no breast tissue at this location. I opened into a cystic cavity as large as an orange, and there were papillary excrescences within it

that suggested cystosarcoma phyllodes or a degenerative fibroadenoma. This particular area was encapsulated and was easily removed once a line of cleavage was established. I did not think it fair to the pathologist to ask for a frozen-section diagnosis.

I should like to back up the statement made by Dr. Talbot regarding excision of breast masses in the female child. I feel very strongly about this. Each year in the Out Patient Department we see a fair number of prepubertal children whose mothers bring them in with a previous diagnosis of tumor or cyst of the breast. In these children, there is usually a discoid subareolar mass, the first sign of mammary development; the mass is identical with that found in young boys of about the same age.

FIGURE 2.

Unfortunately, many of these children have had excision of these masses and subsequently fail to have breast development since the mass represents the anlage.

Our thesis has been that this asymmetry, or indeed the development of fibroadenomas of the breast, represents variations in sensitivity of response of breast tissue to a common stimulus. Characteristically, most women have some asymmetry of breast development and growth. Most of these children who exhibit asymmetrical breast enlargement at puberty eventually have normal breast development.

DR. BENJAMIN CASTLEMAN: The material that we received showed a large amount of stroma surrounding acini and ducts; the glandular elements showed a little infolding with pseudopapillary formation (Fig. 2). Under higher magnification this stroma appeared quite active in places and had a few mitotic figures quite suggestive of a cystosarcoma phyllodes. However, because microscopically there was not much compression of the glandular elements such as is seen in cystosarcoma phyllodes and since there was secretion in the acini, which is not seen in cystosarcoma phyllodes, we believed that this could be virginal hypertrophy. According to Treves and Sunderland,[1] who studied 77 cases of cystosarcoma phyllodes at the Memorial Hospital in New York, secretory activity of the epithelial cells was not observed in any case.

DR. GRANTLEY W. TAYLOR: I should be extraordinarily doubtful that this was just an example of normal hypertrophy because it certainly looked like tumor and I think it must have been tumor. I thought when I read the protocol that it was cystosarcoma phyllodes. We have seen adenofibromas undergo this rapid exaggeration of growth to a very large size without any sarcomatous element — that is usually under the stimulus of pregnancy.

I had one patient, fifteen years of age, who had a carcinoma of the breast that did not follow the general behavior of carcinoma that Dr. Talbot outlined; that patient had a large tumor without skin changes. Preoperatively, we assumed it was a large adenofibroma because the growth was spherical and without any of the characteristic retraction of skin, changes of the nipple or tendency to erode or penetrate the skin. Another point that I think might be alluded to briefly in passing is that in a few cases we have seen a hemangioma of the breast, which under the stimulus of the breast development has itself undergone extraordinary changes because of the increased vascularity. There was one that we saw here some years ago in which the entire breast was a cirsoid mass of tremendously enlarged and engorged tissue. There was no question of that in this case because of the other characteristics.

DR. CASTLEMAN: That patient was a little older and later died of metastases.[2]

A PHYSICIAN: After the tissue was removed, was the breast the same?

DR. NATHANSON: There was very little change. The breast changes have not receded; it is still about the same as it was when I explored the patient eight weeks ago. Mucoid secretion is again coming from the nipple. The nipple is connected with the operative defect. As far as Dr. Taylor's remarks about carcinoma are concerned, at the Beth Israel Hospital in Boston I saw a child ten years of age, as reported by Sears and Schlesinger,[3] who showed the same sort of picture as Dr. Taylor described. She is the youngest patient reported and verified.

DR. TALBOT: I should like to ask Dr. Nathanson how he plans to proceed from here.

DR. NATHANSON: I am following the child very closely. We may have to be more radical if the process progresses. To me, this is more than asymmetrical virginal hypertrophy and is suggestive of a neoplastic lesion such as cystosarcoma phyllodes. The uninvolved breast has developed a good deal, and apparently normally, in the last six weeks. The

patient has had no uterine bleeding since the initial operation.

Addendum

Dr. Castleman: I was not too happy about our diagnosis of hyperplasia and postponed publishing this case until a longer follow-up study was available. As Dr. Nathanson feared, the lesion did progress, and it became obvious that this was not simple hypertrophy. A simple mastectomy was performed several months later and there is no doubt of the diagnosis of cystosarcoma phyllodes of the benign variety. This photograph (Fig. 3) of the cut surface of the lesion shows the characteristic lobulated

Figure 3.

structure separated by deep clefts and cysts, which were filled with gelatinous material. The microscopical appearance was the same as that of the original biopsy. The secretory activity of the epithelial cells, which originally led us away from the diagnosis of cystosarcoma phyllodes, was probably the glandular activity associated with the onset of catamenia and not a part of the tumor. None of the patients in the Memorial Hospital group were as young as this patient. Treves and Sunderland reported 3 patients fifteen to nineteen years of age, all of whose tumors were considered benign.

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CASE 38412

Presentation of Case

An eighty-six-year-old Negress was admitted to the hospital because of pain in the right lower quadrant.

Five days prior to admission the patient had the onset of crampy right-lower-quadrant pain, which increased in severity over the next twenty-four hours and was temporarily relieved by some "white pills" prescribed by her physician. However, the pain recurred, was nonradiating, steady, continuous and sharp and varied somewhat in intensity, but on the whole was quite severe; it was least severe when she lay quietly in bed on her back, and was aggravated by lying on either side and by movement. Anorexia had been present since the onset, and her diet had consisted of coffee and toast. There had been no chills, fever, urinary frequency, dysuria, diarrhea or melena. She had continued to take milk of magnesia daily as had been her custom for years, and had had a daily bowel movement, the last of which occurred the day prior to entry. She had not been nauseated, but on the morning of admission she vomited a small amount of bitter material; since she was blind she was unable to describe the vomitus. The vomiting was accompanied by rather severe crampy abdominal pain.

She had had a hysterectomy for fibroids of the uterus forty years before admission. For two years she had been under the care of her physician because of hypertension; six days prior to the onset of the pain he allegedly had felt a mass in the right side of the abdomen. Her general health had always been good; prior to the onset of pain she had had a good appetite. There had been no previous similar attacks and no gastrointestinal or urinary complaints. There was no known weight loss.

Physical examination revealed a well preserved woman in no acute distress. The lungs were emphysematous. There was a Grade III, blowing, apical systolic murmur. There was an area in the right lower quadrant of the abdomen of increased resistance to palpation and deep in this area of resistance was a smooth, firm, tender mass, which appeared to fill the whole right iliac fossa. There was both direct and rebound tenderness referred to this area. Peristalsis was present. The liver, spleen and kidneys could not be felt. Pelvic and rectal examinations confirmed the tenderness and feeling of fullness in the right lower quadrant.

The temperature was 102°F., the pulse 110, and the respirations 18. The blood pressure was 140 systolic, 95 diastolic.

Examination of the blood revealed a hemoglobin of 12.5 gm. and a white-cell count of 15,400. The urine was normal. A stool gave a negative guaiac reaction. A roentgenogram of the chest demonstrated elevation of the left leaf of the diaphragm, enlargement of the heart, a tortuous calcified aorta and linear areas of density in both lower lung fields. An abdominal film showed an area of haziness in the right middle portion of the abdomen and numerous loops of dilated small bowel in the left side of the abdomen. Barium-enema examination dis-

closed multiple diverticula in the descending colon and sigmoid. The cecum was not completely filled, but there was a suggestion of an extrinsic pressure defect on its medial aspect (Fig. 1). In the intravenous pyelogram the function and structure of the kidneys and urinary tract were normal; the density in the right lower quadrant, with a suggestion of impingement upon the gas shadow of the cecum, and the multiple dilated loops of small intestine in the left side of the abdomen and pelvis were again noted.

FIGURE 1. *Film of Barium-Enema Examination. The arrow points to the medial pressure defect.*

A Harris tube was passed down to the lower ileum, and the patient was given antibiotics and fluid therapy intravenously. There was some decrease in the abdominal pain. The temperature varied between 99.8 and 101°F. The white-cell count was 8000 on the second day and 9500 on the fourth day. On the fourth day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. RICHARD WARREN*: May I see the x-ray films?

DR. CHIU-CHEN WANG: In the films of the chest there are a few strands of basal atelectasis in both lower lung fields. The left leaf of the diaphragm is somewhat elevated. The heart is enlarged, chiefly in the region of the left ventricle. The arch of the aorta is tortuous and calcified. Plain films of the abdomen reveal multiple dilated loops of small bowel principally confined to the left side of the abdomen and a suggestion of a large soft-tissue mass overlying the right lower abdomen. This mass seems to displace the dilated gas-filled loops of small bowel to the left. There are some gas and feces in the rectum.

The intravenous pyelogram shows normal kidneys. The lower pole of the right kidney can be well traced. The right ureter is displaced somewhat to the right, and the right psoas-muscle shadow cannot be so well seen as the left. Barium-enema examination reveals multiple diverticula distributed in the distal colon. A distinct soft-tissue mass is again noted in the right lower quadrant of the abdomen. The cecum — I assume it is the cecum because the terminal ileum is not filled — shows a pressure defect medially (Fig. 1). Spot films of the sigmoid region give no positive evidence of diverticulitis.

DR. WARREN: Would you say that the ureter is displaced laterally or medially?

DR. WANG: Laterally.

DR. WARREN: And the defect in the cecum is an external pressure defect?

DR. WANG: As far as I can tell.

DR. WARREN: One more question about the x-ray films, Would you say that the sigmoid is not over to the right?

DR. WANG: No.

DR. WARREN: In this eighty-six-year-old woman with a mass in the right lower quadrant the number of possibilities is large. From the x-ray films themselves I get a very different impression about the mass than I did from reading the protocol, which states that it occupied the whole iliac fossa. This mass seems to have been higher, more medial to the cecum and nearer the midline than I had been led to believe. I do not wish to make excuses, but I should like to emphasize the obvious fact that by palpating a mass one has a much better idea of where it lies and how fixed it is. Words, no matter how lucid, cannot tell one, and in this elderly patient, whose medical history was possibly not entirely accurate, abdominal palpation was the most important clue to diagnosis. There are degrees between being fixed and being movable that are important in differential diagnosis. For instance, an appendiceal abscess has more prominence and mobility to its outer aspect than a retroperitoneal tumor.

The information given suggests so many possibilities that I shall discuss first those I am fairly sure I can eliminate. According to the x-ray films, the mass did not involve the urinary tract and did not seem to arise in any of the pelvic organs. There was tenderness high on the right side on pelvic and rectal examination, but there was no mass mentioned

*Associate visiting surgeon, Massachusetts General Hospital.

as palpable by these routes. The uterus had been removed. There is no information whether the ovaries were removed at the time of the hysterectomy, but despite this I believe the ovaries are ruled out.

DR. BENJAMIN CASTLEMAN: We looked for the old record, but could not find it. The patient was said to have been operated upon in this hospital.

DR. WARREN: Having dismissed the less likely possibilities, I should like to consider what the mass was doing to the patient. It was not causing intestinal obstruction. During the whole time prior to admission to the hospital she had daily bowel movements, and there was no vomiting until the last day. There were some dilated loops of bowel, but they are compatible with the peritoneal irritation that I am certain this mass was causing.

Whether the peritoneal irritation was caused by infection, infarction or hemorrhage is perhaps the crux of the problem. Let me look at the slim evidence. The white-cell count was 15,000 on admission but fell to normal during the preoperative preparation period of four days. Minimal fever is also against an acute infection. With hemorrhage, one would expect an anemia; the 12.5 gm. of hemoglobin is not much below normal for a woman of this age. I should have liked to have subsequent hemoglobin determinations to confirm that point. Perhaps the vital signs and the course fit an infarcted mass better than either infection or hemorrhage.

Let me discuss the various anatomic sources from which the mass may have originated. Could it have arisen in the bowel? If so, one must seriously consider the appendix since the cecum seems excluded by x-ray examination. A ruptured diverticulum of the cecum is a possibility. These customarily occur in middle life, but this patient's age is no barrier since anything that occurs after the age of eighty-six is unusual! That the patient had diverticulosis of the descending colon is no help in the diagnosis of ruptured diverticulum of the cecum since diverticulosis is acquired and the diverticulum congenital. The possibility of a Meckel diverticulum is good. A Meckel diverticulum producing a mass of this size, however, would be rotated and infarcted and would cause more intestinal obstruction than this patient had. She also had a negative guaiac test on one stool examination, for what that is worth. The question of diverticulitis of the sigmoid over on the right side is something that always has to be considered. I was badly fooled many years ago by such a condition and have been on the lookout for it ever since, but of course, I have not seen it again. Carcinoma of the cecum, the small bowel or the sigmoid seem to be excluded.

What conditions besides those originating in the bowel should I include? Mesenteric cyst, omental cyst and torsion of the omentum are all possibilities. A torsion of a mesenteric or omental cyst is possible; disease of the omentum would be unlikely. It is of great interest, if it was a valid observation, that a physician noted a tumor on a routine examination before the symptoms developed; that would rule out a great many things, such as ruptured appendix, ruptured diverticulum and Meckel's diverticulum.

Could disease of the blood vessels have been present? A mass of this kind causing acute symptoms in an elderly hypertensive woman brings to mind a ruptured mesenteric vessel that had become aneurysmic — so-called mesenteric apoplexy. The patient had symptoms for fifteen days prior to operation, but at no time was pulsation in the mass noted. I am sure that I should have been provided with that information if it had been present. I am going to discard that diagnosis.

Enlarged lymph nodes, inflammatory or lymphomatous mesenteric or retroperitoneal nodes with infarction or hemorrhage, are a real possibility. When I read the protocol originally, I was disposed to rule out a retroperitoneal tumor, but since the ureter seems to have been displaced, I shall have to reconsider that. I think lymphoma or some other type of retroperitoneal tumor should remain in the front of the differential diagnosis, particularly since, according to the x-ray films, the mass was presenting higher and more medially in relation to the cecum than the protocol intimated.

Was this mass metastatic carcinoma from some other region? Although it is possible, there was no obvious source, and I think I should be scraping the bottom of the barrel to bring that in as a differential diagnosis.

A foreign body always has to be considered. People swallow fishbones, which sometimes cause a small perforation in the ileocecal region and lead to an inflammatory mass of this kind; they sometimes end up in the sigmoid. A foreign body may have been left behind at the previous operation, but that type of foreign-body reaction after such a length of time is extremely unlikely.

I shall say that it was probably tumor of the lymph-node variety — a lymphoma in the ileocecal region that had been deprived of its blood supply, had become infarcted and had grown to a fairly large mass.

A PHYSICIAN: Is lymphoma common at the age of eighty-six?

DR. CASTLEMAN: We do not have too many patients at the age of eighty-six. At that age, a lymphoma would be more likely to be of the follicle type, which occurs in elderly people and may produce quite a large abdominal mass in this fashion.

DR. GLENN BEHRINGER: Our opinion on the ward was that this patient had an appendiceal

abscess, and we treated her accordingly for several days without any change in the course; the local pain did not subside, and the fever continued. We believed she should have an exploratory laparotomy, and on the evening of the fourth day we took her to the operating room. Under anesthesia, the mass was palpated higher in the abdomen than had been previously thought; it was at the level of the umbilicus and out of the pelvis, as pelvic examination under anesthesia proved. We changed our diagnosis preoperatively to retroperitoneal tumor.

Clinical Diagnosis

Retroperitoneal tumor.

Dr. Warren's Diagnosis

Retroperitoneal lymphoma with infarction.

Anatomical Diagnoses

Torsion with gangrene of gall bladder.
Cholelithiasis.

Pathological Discussion

Dr. Behringer: On opening of the abdomen after we had aspirated about 500 cc. of serosanguineous fluid, it became obvious that the mass was a gangrenous hollow viscus about 10 to 15 cm. in diameter. On further enlarging the incision we were surprised to find that it was the gall bladder. The anatomy was rather unusual; the patient had a long, dilated gall bladder that was full of stones and was held to the liver by a small mesentery not more than 2.5 cm. in length. The gall bladder had twisted counterclockwise twice on its supporting structures, the small mesentery, the cystic artery and the cystic duct. Cholecystectomy was performed; the patient recovered and has left the ward.

Dr. Castleman: The mass felt six days before the patient had the acute torsion may have been an enlarged gall bladder. Could you tell whether there had been a stone impacted in the duct?

Dr. Behringer: The stones in the gall bladder were quite large, and the duct was tiny. I do not believe that a stone could have passed through the cystic duct.

Dr. Castleman: Sections of the gall bladder showed so much necrosis and gangrene that one would never have recognized it as gall bladder; no muscle tissue could be seen. I am surprised that the gall bladder had not perforated and caused a peritonitis.

Dr. Warren: I should like to ask Dr. Wang if he would revise his interpretation of the displacement of the ureter.

Dr. Wang: It was slightly displaced!

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY
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MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

WHITAKER AND BAXTER BOW OUT

AFTER four years virtually at the helm of AMA's public-relations policy, Whitaker and Baxter, the famed professional team of public-relations counselors, have announced their resignation for the purpose of participating in the presidential campaign. At the same time Dr. Elmer L. Henderson, of Louisville, Kentucky, past president of the American Medical Association and of the World Medical Association, and for four years chairman of the Association's Co-ordinating Committee, which has had the responsibility of supervising Whitaker and Baxter's campaign against socialized medicine, has resigned his chairmanship for the same reason.

As stated in the releases announcing both retirements, the severance was necessary in order that the Association might maintain its ethical and legal status as a nonpartisan, professional organization, utterly aloof from election campaigns "except to join with other nonpartisan groups in urging all eligible voters to cast their ballots on election day, regardless of their affiliations or preferences."

In the heat of the long four-year battle, the representatives of the American Medical Association, speaking through Whitaker and Baxter, — and probably vice versa — have aimed some lusty blows at the current government of, by and for the people, — but that was not done as part of an election campaign.

Whitaker and Baxter, on retiring victorious from the field that their foes have at least temporarily vacated, are leaving behind a host of friends and admirers in the profession and outside it as well. There are, of course, also those who believe — perhaps incorrectly — that both the policies of organized medicine and their fulfillment should be more obviously in the hands of the profession itself.

A JOURNAL AND ITS READERS

IN A note entitled "The Content of Science" in a recent issue of *Science*,* the chairman of the Editorial Board of the American Association for the Advancement of Science indicated the policies of the journal regarding the subject matter, scientific specialties and length of the manuscripts accepted for publication. The belief was expressed that "the dearth of articles in certain fields does not reflect a bias on the part of the editors, but rather the failure of some scientists to appreciate the fact that *Science* offers an outlet for quick publication of significant research. . . ."

This notice suggested to the editors of the *New England Journal of Medicine* that perhaps a similar statement should be made with reference to this publication.

The *New England Journal of Medicine* has never relinquished its original function of serving the general medical reader, a function that has been brought into increasing prominence in recent years, as its circulation has expanded. Although published in New England and inheriting the New

*Meyerhoff, H. A. Content of Science. *Science*, 115:3, 1952.

England medical tradition, it is not for New England readers only, for it now reaches, in addition to the nearly 7,000 members of the Massachusetts and New Hampshire medical societies, some 19,000 independent subscribers in all parts of the world. Such a body of readers obviously has varying interests, which it is the desire of the editors to meet as fully and as well as possible.

The most prominent feature of any journal is its original papers, most of which, except in a few planned publications, are voluntarily submitted. Papers selected for publication by the *Journal's* board of editors are evaluated on the basis of originality, scientific accuracy, general usefulness and literary excellence — and without knowledge of the authors' identity.

Obviously, few papers will be of universal interest to all the *Journal's* readers; the goal of the editors is the selection of a variety of material that will satisfy a diversity of tastes and at the same time keep the reader abreast of the important advances in medicine; many of our readers are specialists who subscribe to the *New England Journal of Medicine* to learn about other specialties.

Short papers are in the main better adapted to publication than long ones, and the relatively few pages of a weekly journal are scarcely suitable for the presentation of long monographs. It must be emphasized, however, that a function of a journal such as this is to present the results of original investigations and observations in *any* field that pertains to medicine. Early publication is made possible by the weekly nature of the *Journal*, by the fact that it purposely avoids a "backlog," and by the possibilities offered for publication of preliminary notes in the section entitled "Medical Intelligence."

This department, revived after many years of suspended animation, is intended to serve a somewhat flexible purpose. Here are published *brief* clinical notes, reports of unusual cases, descriptions of new methods and instruments and a variety of other matter of more or less absorbing interest.

The articles on Medical Progress, which have achieved a deserved popularity, are solicited after a careful consideration of subjects and authors by the editorial board. Although this is a planned series, unsolicited contributions are occasionally accepted.

The Case Records of the Massachusetts General Hospital need no special comment. Developed as a method of instruction by Dr. Richard C. Cabot nearly sixty years ago, they were first published independently in 1911; for nearly thirty years they have comprised one of the *Journal's* most valued features.

Needless to say, a journal's correspondence column is in the hands of its readers. Contributions to this section are always welcome.

Finally, as the editor of *Science* phrased it, the *Journal* "is not so much what the editorial board and its editors would like it to be, as what its contributors make it."

PREVENTION OF GONORRHEA

PENICILLIN has now been in general use for the treatment of gonorrhea for eight or nine years. For the greater part of this time it has been the major or the only form of therapy for this disease in almost all large clinics and by almost all physicians. From available evidence it seems likely that the therapeutic efficacy of penicillin in gonorrhea has been retained unchanged throughout this period and that penicillin-resistant strains of gonococci have not yet appeared — at least none have been established.

This is in sharp contrast to the situation that prevailed a few years after the sulfonamides were introduced and gained wide usage. Clinical failures from sulfonamide therapy of gonorrhea soon became common, and sulfonamide-resistant strains of gonococci began to appear in rapidly increasing numbers so that only a small proportion of strains are now susceptible to those drugs. The basis for this difference may reside, in large measure, in the marked variation in susceptibility of strains of gonococci to these two agents; they are all highly sensitive to penicillin whereas they are relatively much less sensitive to sulfonamides. This was true when both these agents were first introduced and is, of course, all the more true today.

The use of the sulfonamides in the programs of mass chemoprophylaxis during World War II has also resulted in the appearance and rapid dissemination of sulfonamide-resistant strains of Group A hemolytic streptococci. In that instance, serious epidemics of infections with some specific types of

sulfonamide-resistant hemolytic streptococci occurred in areas and among troops where mass chemoprophylaxis was carried out.

Because of these experiences with the sulfonamides there has been some reluctance to undertake large-scale prophylactic programs with penicillin or other useful antimicrobial agents. The report of the Navy's experience* over a period of three years with the oral use of penicillin as a prophylaxis of gonorrhea is therefore of considerable interest. In this program the penicillin was not used continuously, as in the mass chemoprophylaxis with sulfonamides employed during the war. Instead, the penicillin was given intermittently within a short time of each actual or potential exposure. It was therefore more correctly abortive treatment rather than prophylaxis.

In the Navy's experience penicillin given by mouth in doses of 250,000 units within a few hours of exposure was nearly 100 per cent effective in preventing gonorrhea. This was more readily accepted by the Navy personnel than either mechanical or local chemical prophylaxis, but usage varied with the emphasis given by the medical officers, some of whom actually discouraged its use on theoretical grounds. The efficacy of this procedure has remained unchanged after three years, and resistant strains of gonococci have not been encountered. It is considered extremely improbable that this method of administration will have any influence on the development of resistant forms of either the gonococcus or of *Treponema pallidum*.

The data from the Navy suggest that doses of 250,000 units of penicillin by mouth may also prevent syphilis, but this is not dependable and will almost certainly fail if the victim receives a heavy inoculum. There has been no indication of altering or masking the evolution of primary and secondary lesions of syphilis in those whom it fails to protect. It has not produced any increase in frequency of latent syphilis, as seen by serologic follow-up examinations, total cases, and a special analysis of each latent case during 1950, but further investigations of this aspect are required.

The report also shows that this usage of penicillin tends to abandonment of mechanical and chemical prophylactic methods if indoctrination is careless. This, in turn, leads to increase of other venereal diseases — chancroid, nongonococcal urethritis and, if extreme, syphilis as well. It is believed, however, that such carelessness can be largely overcome.

Sensitization and sensitivity reactions to penicillin have not been much of a problem. In most cases, reactions have been mild and have occurred after the patient took the first tablet. The severe penicillin reactions that have been reported have almost all been clearly due to intramuscular usage and have followed sensitization through intramuscular injections. Impressions that the oral use of penicillin caused sensitization have not been confirmed according to this report.

As a result of the analysis of this experience, the Preventive Medicine Division of the Navy recommends penicillin tablets containing 250,000 units as a prophylactic measure against gonorrhea, but only in areas of high incidence and with proper indoctrination in their limitations.

*Babione, R. W., Hedgecock, L. E., and Ray, J. P. Navy experience with oral use of penicillin as prophylaxis. *U. S. Armed Forces M. J.* 3: 973-990, 1952.

NEXT!

STUDIES now under way at the clinics of the University of Chicago may revolutionize the private practice of medicine (from the patient's viewpoint), relieve the tedium of the doctor's waiting room and relegate last year's files of *Life* and the *New Yorker* to the Boy Scout paper collection.

These investigations, according to the July, 1952, issue of the *Journal of Medical Education*, have as their chief purpose the selection of those types of films that will have the greatest appeal to a general audience, such as is found in the outer office of any general practitioner of medicine. The purpose is to make the patient's cooling-off period not merely more endurable, but of positive benefit to him by means of a continuous moving-picture program, "ranging from instructive cartoons to films of more formal educational value."

The idea in itself, let alone its fulfillment, suggests that after all the American way of life is the American way of life. There could be presented to a captive audience all the arguments against socialized medicine without the nuisance of an attempted rebuttal, the advantages of dental chlorophyll presented in a Mickey Mouse extravaganza, or a trav-

elogue of American doctors on their annual summer pilgrimage to Europe, rates of exchange being what they are.

A portable machine is already available that, equipped with a continuous film, dispenses with the services of an operator and avoids labor complications. The only interruption would be from the doctor himself, as he bowed his patients in and out of the consulting room.

Believers in spiritual rappings are running mad in Boston, as in many other places. It is becoming extremely lucrative business to the mediums, usually young ladies, who are turning their rapping talents into dollars very rapidly.
Boston M. and S. J. *Oct. 13, 1852*

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Georgetown University School of Medicine, 1940.

SCHIMMEL, MILTON ROBERT, 117 Pleasantview Avenue, Longmeadow.
College of Physicians and Surgeons, Kansas City, 1944. Sponsor: Dr. Alfonso A. Palermo, 121 Chestnut Street, Springfield.

SELDEN, LAWRENCE VAN, 21 Copeland Street, Springfield.
Tulane University School of Medicine, 1945.

WETHERBEE, DONALD GIST, 70 Woodside Terrace, Springfield.
Harvard Medical School, 1946.

WILLIAMS, HAROLD BRECKER, 228 College Street, Springfield.
Albany Medical College, 1947.

ALLEN G. RICE, M.D., *Secretary*
33 School Street, Springfield

HAMPSHIRE

SHARPE, MEYER, 24 West Center Street, Florence.
Harvard Medical School, 1944.

Joseph R. Hobbs, M.D., *Secretary*
Main Street, Williamsburg

MIDDLESEX EAST

ALFANO, BLAISE FRANCIS, 4354 Washington Street, Roslindale.
Tufts College Medical School, 1950.

KAKNES, GEORGE BYRON, 65 High Street, Woburn.
Tufts College Medical School, 1945.

CODIN, KENNETH, 28 High Street, Stoneham.
Middlesex University School of Medicine, 1941. Sponsor: Dr. James Devine, 17 Arlington Road, Woburn.

William F. Hickey, Jr., M.D., *Secretary*
15 Dix Street, Winchester

MIDDLESEX NORTH

ST. JEAN, ALBERT HENRI, 346 Princeton Blvd., Lowell.
College of Physicians and Surgeons, Kansas City, 1942. Sponsor: Dr. Artemas J. Stewart, 310 Merrimack Street, Lowell.

GAIESKI, BENJAMIN JOSEPH, 195 Nesmith Street, Lowell.
Tufts College Medical School, 1945.

SWEENEY, FELIX ALBERT, 121 Eleventh Street, Lowell.
Tufts College Medical School, 1947.

Philip G. Berman, M.D., *Secretary*
174 Central Street, Lowell

MIDDLESEX SOUTH

BOLES, RUSSELL SAGE, JR., 36 Gray Street, Cambridge.
Columbia University College of Physicians and Surgeons, 1946.

GREEN, SIDNEY, 1935 Beacon Street, Waban.
Tufts College Medical School, 1946.

HAMLIN, ROBERT HENRY, 1529 Massachusetts Avenue, Cambridge.
Northwestern University Medical School, 1947.

LA BELLA, CHARLES DANTE, JR., 324 Boston Avenue, Medford.
College of Physicians and Surgeons, Kansas City, 1943. Sponsor: Dr. Laurence J. Golden, 33 Winthrop Street, Medford.

LAWRENCE, FRED EUGENE, 2 Belton Street, Arlington.
Washington University School of Medicine, 1944.

LEIGH, KENNETH EDWIN, 46 Garden Circle, Waltham.
Tufts College Medical School, 1951.

MALOOF, CLARENCE CALILE, 90-1 Middlesex Road, Waltham.
Tufts College Medical School, 1945.

NASH, HAROLD E., JR., 23 Bellvista Road, Brighton.
Tufts College Medical School, 1945.

ROMEO, Salvatore Nicholas, 294 Huron Avenue, Cambridge.
Missouri College of Medicine, 1927. Sponsor: Dr. Leo T. Myles, 60 Brattle Street, Cambridge.

SKINNER, JAMES C., 29 Holden Wood Road, Concord.
Harvard Medical School, 1946.

SPRINGER, FRANK LESLIE, 188 Quinobequin Road, Waban.
Boston University School of Medicine, 1936.

WRIGHT, ROGER HOWARD, 181 Summer Street, Arlington.
Harvard Medical School, 1949.

Alexander A. Levi, M.D., *Secretary*
481 Beacon Street, Boston

MIDDLESEX WEST

BETINIS, WILLIAM JOHN, Union Street, Marlboro.
Albany Medical College, 1946.

GALE, JOHN S., 14 Clark Street, Framingham.
McGill University Faculty of Medicine, 1947.

JOHNSON, ROBERT EDMOND, 35 Winter Street, Framingham.
Columbia University College of Physicians and Surgeons, 1945.

LAMOTHE, PAUL ALBERT, 37 Main Street, Framingham.
Tufts College Medical School, 1945.

WHEELER, JOHN STUART, 67 Washington Street, Natick.
New York Medical College, 1946.

John J. Lepore, M.D., *Secretary*
96 W. Main Street, Marlboro

NORFOLK

AVERILL, JAMES HALSEY, 57 Lawton Road, Needham.
Harvard Medical School, 1946.

BANTON, HUSTON J., 46 Linnet Street, West Roxbury.
University of Illinois College of Medicine, 1927.

BEVIVINO, BRUNO JOSEPH, 7 Fales Road, Dedham.
College of Physicians and Surgeons, Kansas City, 1941. Sponsor: Dr. Archie Abrams, 203 Commonwealth Avenue, Boston.

BOWERS, JOHN THOMAS, JR., 987 South Street, Roslindale.
Boston University School of Medicine, 1946.

BUNKER, ROBERT BREWSTER, 45 Clapboardtree Street, Westwood.
Columbia University College of Physicians and Surgeons, 1948.

BURKE, LOUIS, 40 Stetson Street, Brookline.
Tufts College Medical School, 1944.

CONTOMPASIS, PETER HARRY, 4459 Washington Street, Roslindale.
Tufts College Medical School, 1947.

DALRYMPLE, WILLARD, 4 Bay View Road, Wellesley.
Harvard Medical School, 1946.

DRISCOLL, ROBERT ANTHONY, 5 Cliff Road, Milton.
Tufts College Medical School, 1946.

GILCHRIEST, BERNARD NORBERT, 31 Nottingham Street, Dorchester.
Tufts College Medical School, 1944.

GORBACH, ARTHUR CHESTER, JR., 75 Outlook Drive, Lexington.
Western Reserve University School of Medicine, 1945.

JONES, CHARLES WILLIAM, 329 Nichols Street, Norwood.
University of Vermont College of Medicine, 1945.

KAUFMAN, IRVING, 422 Centre Street, Jamaica Plain.
College of Physicians and Surgeons, Boston, 1941. Sponsor: Dr. Henry Cabitt, 520 Beacon Street, Boston.

LANE, GEORGE MARTIN, 21 Alton Court, Brookline.
College of Physicians and Surgeons, Boston, 1944. Sponsor: Dr. Henry J. Bakst, 285 Clinton Road, Brookline.

LEBARON, FRANCIS E., 56 South Street, Foxboro.
Middlesex University School of Medicine, 1935. Sponsor: Dr. Valmore Pelletier, Cottage Street, Norwood.

LIPOFSKY, DAVID, 527 Gallivan Boulevard, Dorchester.
College of Physicians and Surgeons, Kansas City, 1938. Sponsor: Dr. Joseph Newman, 40 American Legion Highway, Dorchester.

MACKENZIE, JOHN MUNRO, 591 Morton Street, Dorchester.
Queens University Faculty of Medicine, 1943.

MAGRUDER, MARGARET BATES, 119 Gerry Road, Chestnut Hill.
Tufts College Medical School, 1944.

McCARTY, KEVIN JOHN, 989 South Street, Roslindale.
Georgetown University School of Medicine, 1950.
O'CONNOR, ARTHUR JOSEPH, 33 Brookdale Street, Roslindale.
Tufts College Medical School, 1950.
STRONG, MERVYN STUART, 73 Dean Road, Brookline.
Trinity College, Dublin, 1947. Sponsor: Dr. Leighton F. Johnson, 29 Bay State Road, Boston.
WINER, BERTRAM MURRAY, 38 Harvard Avenue, Brookline.
New York Medical College, 1946.

S. L. SKVIRSKY, M.D., *Secretary*
278 State House, Boston

NORFOLK SOUTH

CROSS, MORRIS CARDONE, 160 North Main Street, Randolph.
Middlesex University School of Medicine, 1934. Sponsor: Dr. Isadore Schwartz, 1079 Hancock Street, Quincy.
HAZEN, LLOYD NORMAN, 1720 Commercial Street, East Weymouth.
University of Vermont College of Medicine, 1946.
TWIBLE, ELLSWORTH ARNOLD, 58 Fairlawn Avenue, North Weymouth.
Boston University School of Medicine, 1948.

Ebenezer K. Jenkins, M.D., *Secretary*
Norfolk County Hospital, South Braintree

PLYMOUTH

GRAY, BARBARA HUGHES, 219 Main Street, North Easton.
University of Oklahoma School of Medicine, 1942.
MURPHY, THOMAS JOSEPH, 152 West Street, Brockton.
Yale University School of Medicine, 1946.
WELCH, EDWARD KENNETH, 655 Washington Street, Whitman.
University of Vermont College of Medicine, 1951.
WRIGHT, ROBERT FRANCIS, 29 Kingman Street, Brockton.
Boston University School of Medicine, 1946.

Samuel Gale, M.D., *Secretary*
12 Cottage Street, Brockton

SUFFOLK

ALTMAN, GEORGE ELIOT, 206 Clark Road, Brookline.
Tufts College Medical School, 1946.
BERG, ROBERT LEWIS, 56 Mt. Vernon Street, Boston.
Harvard Medical School, 1943.
BOYLE, JOSEPH AUGUSTINE, 574 Newbury Street, Boston.
Tufts College Medical School, 1949.
COFFIN, SCOTT FARNUM, JR., 29 Edgehill Road, Brookline.
University of Rochester School of Medicine, 1943.
DECKER, JOHN PAUL, 178 Commonwealth Avenue, Boston.
Jefferson Medical College, 1946.
ELLISTON, WILLIAM ARTHUR, 263 South Avenue, Weston.
University of Cambridge Faculty of Medicine, England, 1934. Sponsor: Dr. Theodore B. Bayles, 1180 Beacon Street, Brookline.
EWALT, JACK RICHARD, 745 Trapelo Road, Waltham.
University of Colorado School of Medicine, 1933.
GABUZDA, GEORGE JOSEPH, 19 Egleton Park, Winthrop.
Harvard Medical School, 1944.
GAIR, DONALD SUAL, 101 Fenwood Road, Boston.
Harvard Medical School, 1950.
GREELEY, DAVID MCLEAN, 58 Country Club Road, Newton Centre.
Harvard Medical School, 1937.
GRIFFIN, BELTON GLENN, 237 West Street, Needham.
Tulane University School of Medicine, 1944.
HABIB, HALIM GEORGE, 129 Warren Avenue, Boston.
Tufts College Medical School, 1946.
HAYES, MARJORIE, 75 Chestnut Street, Boston.
Johns Hopkins University School of Medicine, 1942.
HUTCHESON, BELLENDEN RAND, 3 Goodwin Place, Boston.
Northwestern University Medical School, 1947.
LOVELL, CHARLES VIVIEN DUBOUCHET, 504 Beacon Street, Boston.
Harvard Medical School, 1943.
LYNCH, ALBERT EDWARD, 15 Forest Street, Cambridge.
Tufts College Medical School, 1947.
MACDONALD, GEORGE EDMOND, 390 Weld Street, West Roxbury.
Harvard Medical School, 1945.
MACMILLAN, ALEXANDER STEWART, 108 Mt. Vernon Street, Boston.
Harvard Medical School, 1946.
MALOOF, FARAKE, 22 Lowe Street, Quincy.
Tufts College Medical School, 1945.
MODELL, ARNOLD H., 6 Travis Road, Natick.
Long Island College of Medicine, 1947.
NACHLAS, MARVIN MORTON, 31 Dundee Road, Arlington Heights.
Johns Hopkins University School of Medicine, 1943.
PHELAN, JOHN VINCENT, JR., 74 Horadan Way, Roxbury.
Tufts College Medical School, 1947.
QUARTON, GARDNER COWLES, Weston Road, Lincoln.
Harvard Medical School, 1944.
REED, GEORGE FARRELL, 3 Morley Street, Needham.
Syracuse University College of Medicine, 1946.
RELMAN, ARNOLD SEYMOUR, 471 Beacon Street, Boston.
Columbia University College of Physicians and Surgeons, 1946.
REYNOLDS, ROBERT NELSON, 55 Revere Street, Boston.
Albany Medical College, 1946.
SCHRAFFA, FRANCIS PAUL, 149 Putnam Street, East Boston.
Middlesex University School of Medicine, 1936. Sponsor: Dr. G. Lynde Gately, 624 Bennington Street, East Boston.
SEARS, BERNARD RICHTER, 416 Marlboro Street, Boston.
Tufts College Medical School, 1944.
SELVERSTONE, LOUIS ALBERT, 1737 Cambridge Street, Cambridge.
Harvard Medical School, 1944.
SMITH, STEPHEN, III, 18 Springdale Avenue, Wellesley Hills.
Cornell University Medical College, 1943.
STARKEY, GEORGE WALLACE BAILEY, 10 Ingraham Road, Wellesley.
Harvard Medical School, 1943.
TOBIAS, GERD JAMES, 171 Harrison Avenue, Boston.
University of California Medical School, 1946.
WILKINS, EARLE WAYNE, JR., 64 Grant Avenue, Watertown.
Harvard Medical School, 1944.

Charles G. Shedd, M.D., *Secretary*
1180 Beacon Street, Brookline

WORCESTER

ANDERSON, ROBERT IRVING, Worcester City Hospital, Worcester.
Tufts College Medical School, 1948.
CATALDO, LEWIS JOSEPH, JR., 398 June Street, Worcester.
Tufts College Medical School, 1946.
GARDNER, PAUL JOSEPH, 23 Varnum Street, Worcester.
Boston University School of Medicine, 1947.
HESTER, RAY DANIEL, South Street, West Warren.
College of Physicians and Surgeons, Boston, 1934. Sponsor: Dr. Meyer H. Haight, Warren.
HIGANO, NORIO, 8 Alden Avenue, Shrewsbury.
St. Louis University School of Medicine, 1945.
JACQUES, LEO CHARLES, 3 Perry Street, North Grafton.
Georgetown University School of Medicine, 1941.
LEDONNE, JOHN E., 60A Elm Street, Worcester.
Tufts College Medical School, 1946.
LIDSTONE, FREDERICK BARTLETT, 15 Asceola Avenue, Worcester.
Tufts College Medical School, 1947.
VARJABEDIAN, ANTHONY, 76 Elm Street, Worcester.
Yale University School of Medicine, 1944.
VERRILLI, ROCCO ANTHONY, Aldrich Street, Webster.
Albany Medical College, 1951.

Paul Bergin, M.D., *Secretary*
57 Cedar Street, Worcester

DEATH

SPROULL — John Sproull, M.D., of Haverhill, died on September 18. He was in his seventy-eighth year.

Dr. Sproull received his degree from Boston University School of Medicine in 1901. He was a member of the staff of Hale Hospital and of the American Roentgen Ray Society, New England Roentgen Ray Society and Radiological Society of North America, and a fellow of the American College of Radiology and American Medical Association.

He is survived by his widow, a daughter, a sister and three brothers.

NOTICES

ANNOUNCEMENT

Dr. Harold W. Rubin announces the removal of his office to 1093 Beacon Street, Brookline 46, for the practice of obstetrics and gynecology.

CARDIAC WORK CLASSIFICATION UNIT

The Cardiac Work Classification Unit, sponsored by the Massachusetts Heart Association and located at the Bay State Medical Rehabilitation Clinic, 255 Charles Street, Boston, on the grounds of the Massachusetts General Hospital, is now in operation for the evaluation of suitability for work or rehabilitation training for employment of cardiac patients.

Patients will be accepted only on recommendation of a physician or clinic. Details regarding methods and operation were published in the *Journal* for August 21. Clinic sessions are held on Thursday evenings. Patients are accepted regardless of financial status but will be expected to pay the portion of costs of which they are capable.

Application blanks and further information may be obtained on telephone (LAfayette 3-2667) or written request.

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the Bigelow Amphitheater of the White Building (3-A), Massachusetts General Hospital, on Tuesday, October 14, at 8 p.m. The following program will be presented by the Department of Surgery of the Massachusetts General Hospital, Dr. E. D. Churchill presiding:

Metabolic Rate and Thyroid Function Following Acute Thermal Trauma in Man. Drs. George L. Nardi, Richard L. Rovit and Manuel Quijano.

The Ebb and Flood of the Eosinophils in the Burned Patient and their Use in the Clinical Management. Drs. Anne Wight, John W. Raker and William R. Merrington.

Adrenal Hormones and Increased Capillary Permeability of Burns — An Experimental Evaluation. Drs. Anne Wight, Philip Weisman and Richard L. Rovit.

Observations on the Conditions Governing the Emptying of the Stomach in Man. Drs. William Waddell and C.-C. Wang.

Metabolic Changes Associated with Eck Fistula in Man. Dr. William McDermott.

Our Experience with 34 Cases of Cushing's Disease. Drs. John W. Raker and Oliver Cope.

FOURTH ANNUAL CONFERENCE ON ALCOHOLISM

The fourth annual Conference on Alcoholism, on the subject, "Alcoholism and Public Action," will be held on Wednesday, October 22, at John Hancock Hall, Boston, from 1 to 10 p.m. The Conference will be held under the auspices of the Boston Committee on Alcoholism.

Dinner, including registration, is $4.50. Registration to attend lectures only is $1.00. Reservations may be made with the Boston Committee on Alcoholism, Room 525, 419 Boylston Street, Boston (telephone KEnmore 6-1954).

NORFOLK DISTRICT MEDICAL SOCIETY

The November meeting of the Norfolk District Medical Society, will be held in John Ware Hall, Boston Medical Library, 8 Fenway, on Tuesday, November 25, at 8 p.m. Dr. Franz J. Ingelfinger will speak on the subject, "Dietary Treatment of Gastroenterologic Disorders."

SOUTH END MEDICAL CLUB

A meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, October 21, at 12 noon.

Dr. Frank P. Foster, of the Department of Internal Medicine, Lahey Clinic, and a member of the staffs of the New England Deaconess and New England Baptist hospitals, will speak on the subject, "Functional Menstrual Disorders and Their Management with Particular Reference to Hormone Therapy." Lantern slides will be shown.

All physicians are cordially invited to attend.

NEW YORK SOCIETY FOR CIRCULATORY DISEASES

The fifth regular meeting of the New York Society for Circulatory Diseases will be held in Room 20 of the New York Academy of Medicine building, on Tuesday, October 14, at 8:30 p.m. The entire program, devoted to a symposium on critical evaluation of graphic registrations in cardiology, has been dedicated as the second memorial tribute to the first president of the American College of Cardiology, Dr. Franz M. Groedel. During the meeting there will be an exhibit in collaboration with the Rare Book Department of the Library of the New York Academy of Medicine. Apparatus from the collection of Dr. Philip Reichert will also be shown to illustrate the history of graphic registration. A detailed program may be obtained from Gabriel F. Greco, M.D., secretary, 114-08 Linden Boulevard, Ozone Park 16, New York.

NEW YORK TUBERCULOSIS AND HEALTH ASSOCIATION

An all-day meeting and dinner session of the New York Tuberculosis and Health Association will be held on Friday, November 21, at the Hotel Statler, New York City. The program will emphasize progress made during the fifty years of the Association's organized drive against tuberculosis and point up the task ahead.

AMERICAN CANCER SOCIETY

The annual meeting (scientific session) of the American Cancer Society will be held at the Park Sheraton Hotel, New York City, October 21 and 22. The general topic of the session will be "Radiation versus Cancer: A critical evaluation."

The first day of the program will include discussions on the following subjects: "X-Rays As Diagnostic Tools"; "Fundamentals in Radiation Therapy"; and "Practical Applications of Irradiation in the Treatment of the Cancer Patient." The second day will be devoted to a round-table discussion of end results in the treatment of uterine cancer, as well as lectures on irradiation in cancer of the breast and head and neck (excluding the larynx), rotation therapy, high-energy electron accelerators and radium and radioactive isotopes, the final discussion being concerned with means of interesting young physicians in a career of therapeutic radiology.

HOSPITAL FOR JOINT DISEASES

The annual conference of the alumni of the Hospital for Joint Diseases in New York will be held at the hospital on October 30 and 31 and November 1.

The day and evening of October 30 will be taken over entirely by Dr. Joseph Trueta, Nuffield Professor of Orthopedic Surgery, of Oxford University, England.

On the morning of October 31, Dr. Anthony F. DePalma, professor of orthopedic surgery, Jefferson Medical College, Philadelphia, will conduct a panel discussion on the subject of the shoulder-neck pain syndrome.

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE

The annual meeting of the Association for Research in Nervous and Mental Disease will be held at the Hotel Roosevelt, New York City, on December 12 and 13. The subject of the meeting will be "Metabolic and Toxic Diseases of the Nervous System."

ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES

The fifty-ninth annual meeting of the Association of Military Surgeons of the United States will be held at the Statler Hotel, Washington, D. C., November 17-19, under the presidency of Major General Harry G. Armstrong, Surgeon General of the Air Force. Point credits for retirement will be given all eligible reserve officers attending the scientific session.

President Truman has been invited to speak at the traditional banquet of the Association on the evening of November 19.

NATIONAL SOCIETY FOR CRIPPLED CHILDREN AND ADULTS

The twenty-ninth annual convention of the National Society for Crippled Children and Adults will be held at the Fairmount Hotel, San Francisco, October 26-29.

AMERICAN PUBLIC HEALTH ASSOCIATION

The eightieth annual meeting of the American Public Health Association will be held in Cleveland, Ohio, October 20–24.

The annual banquet will be held on Thursday evening October 23, with Dr. Brock Chisholm, director general of the World Health Organization, as speaker. His subject will be "Human Relations in World Health."

INTERNATIONAL MEDICAL ASSEMBLY

The thirty-seventh International Medical Assembly will be held in the Public Auditorium, Cleveland, Ohio, November 10–13. The program will include lectures, clinics and scientific and technical exhibits.

EIGHTH INTERNATIONAL CONGRESS ON RHEUMATIC DISEASES

The Eighth International Congress on Rheumatic Diseases will be held at Geneva, Switzerland, and Aix-les-Bains, France, August 24–28, 1953. In addition to a scientific program presented by international figures in the treatment of rheumatic disease, there will be technical and scientific exhibits, and scientific motion pictures will be shown.

Further information may be obtained from Professor Karl M. Walthard, Institut de Physiatrie, Hôpital Cantonal, Geneva, Switzerland.

SOCIETY MEETINGS AND CONFERENCES

October 6–December 8 and March 2–May 4. Massachusetts Department of Mental Health. Post-graduate Seminar in Neurology and Psychiatry. Page 540, issue of October 2.

October 7–December 9. Massachusetts Department of Mental Health. Course in Child Psychiatry (Pediatric Neuropsychiatry). Page 540, issue of October 2.

October 9–11. American Association of Blood Banks. Page 497, issue of September 25.

October 11–29. Springfield Hospital Educational Program. Page 497, issue of September 25.

October 14. Springfield Academy of Medicine. Page 190, issue of July 31.

October 14. Harvard Medical Society. Page 583.

October 14. New York Society for Circulatory Diseases. Page 583.

October 15–April 8. Postgraduate Medical Institute. Page 452, issue of September 18.

October 18–23. American Academy of Pediatrics. Page xi, issue of July 24.

October 20–24. American Public Health Association. Notice above.

October 21. South End Medical Club. Page 583.

October 21 and 22. American Cancer Society. Page 583.

October 22. Fourth Annual Conference on Alcoholism. Page 583.

October 26–29. National Society for Crippled Children and Adults. Notice above.

October 27–29. Medicomilitary Symposium. Page 454, issue of September 18.

October 28–30. New England Postgraduate Assembly. Hotel Statler, Boston.

October 29. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

October 30. New England Pathological Society. Page 540, issue of October 2.

October 30–November 1. Hospital for Joint Diseases. Page 583.

October 30–November 1. National Association for Music Therapy. Page ix, issue of July 31.

October 31 and November 1. Eastern Section of American Trudeau Society. Page 190, issue of July 31.

November 2–7 and 10–21. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

November 9 and 10. American Society for the Study of Arteriosclerosis. Page 78, issue of July 10.

November 10–13. International Medical Assembly. Notice above.

November 11–14. American Society of Anesthesiologists, Inc. Third Annual Refresher Course Program. The Bellevue-Stratford, Philadelphia.

November 17–19. Association of Military Surgeons of the United States. Page 583.

November 18, February 6 and April 3. New England Society of Anesthesiologists. Page 418, issue of September 11.

November 21. New York Tuberculosis and Health Association. Page 583.

November 25. Norfolk District Medical Society. Page 583.

December 12 and 13. Association for Research in Nervous and Mental Disease. Page 583.

August 24–28, 1953. Eighth International Congress on Rheumatic Diseases. Notice above.

District Medical Societies

MIDDLESEX SOUTH

October 29. 11:15 a.m. Mount Auburn Hospital, Cambridge.

NORFOLK

October 28.
November 25.
January 27.
February 24.
March 24.

Calendar of Boston District for the Week Beginning Thursday, October 16

Thursday, October 16

*8:30–10:00 a.m. Orthopedic Staff Conference, Boston City Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. The Surgical Treatment of Bleeding Esophageal Varices. Dr. Robert R. Linton. Stearns Auditorium, New England Center Hospital.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

Friday, October 17

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit. 57 East Concord Street.
*10:00 a.m.–1:00 p.m. Medical and Surgical Grand Rounds. Dr. George W. Thorn and Dr. Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m.–1:00 p.m. Combined Medical and Surgical Rounds. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Diabetes Lecture. Dr. Elliott Joslin. New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*7:00–9:00 p.m. Combined Anesthesia Teaching Conferences of Boston. Amphitheater, Evans Memorial, Massachusetts Memorial Hospitals, Eighth Floor, 65 East Newton Street, Boston.

Saturday, October 18

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

Monday, October 20

*8:00–9:00 a.m. Combined Medical and Surgical Rounds for Diabetic Surgery Cases. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building. Boston City Hospital.
12:00 m. Pediatric Medical-Surgical Conference (Boston Floating Hospital). Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Endocrine Conference. Dr. Astwood. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*2:00–4:00 p.m. Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital, Waltham.
*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

Tuesday, October 21

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
*12:00 m. South End Medical Club. Headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue.
*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Surgical Pathological Conference. Pratt Diagnostic Clinic, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*6:00–9:30 p.m. Course in Child Psychiatry (Pediatric Neuropsychiatry). Metropolitan State Hospital, Waltham.

Wednesday, October 22

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Medical Conference. (Children's Medical Center.) Jimmy Fund Building, 25 Binney Street.
12:00 m. Weekly Pathological Meeting. Joslin Amphitheater, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Neurology Conference. Dr. Adams. Stearns Auditorium, New England Center Hospital.
1:00–10:00 p.m. Fourth Annual Conference on Alcoholism. John Hancock Hall.
*4:00 p.m. Thoracic Conference. Held by Overholt Clinic, Harris Hall, New England Deaconess Hospital.
*4:00–5.30 p.m. Fracture Lecture. Boston City Hospital.

*Open to the medical profession.